Anticonvulsants

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Barbiturates									
primidone (Mysoline®) [1]	generic			X§	X§				
phenobarbital [2]	generic		X	X§	X§				
Hydantoins									
ethotoin (Peganone®) [3]	Ovation			X§	X§				
phenytoin ER (Dilantin®) [4]	generic, Pfizer			X§	X§				
phenytoin ER (Phenytek®) [5]	Mylan								
Succinimides									
ethosuximide (Zarontin®) [6]	generic	X§							
methsuximide (Celontin®) [7]	Pfizer	X§							
Benzodiazepines									
clobazam (Onfi™) [8]	Lundbeck						X*§		
clonazepam (Klonopin®) [9]	generic	X§	X§				X§		
diazepam rectal gel (Diastat®) [10]	generic			X*§	X*§				

* Indicates approval for adjuvant therapy only

§ Adult and Pediatric Indication

Other Indications:

Phenobarbital is indicated as a sedative for the relief of anxiety, tension, and apprehension.

Phenobarbital is indicated for insomnia, although the barbiturates are no longer used for this indication.

Phenobarbital is also indicated for treatment of status epilepticus; however, its full antiepileptic effect is not immediate. Intravenous benzodiazepines should be given initially for status epilepticus.

Phenytoin (Dilantin, Phenytek) is indicated for prevention and treatment of seizures occurring during or following neurosurgery.

Clonazepam (Klonopin) is indicated for panic disorder.

Diazepam rectal gel (Diastat) is indicated for the management of selected, refractory patients on stable regimens of anti-epileptic agents who require intermittent use of diazepam to control bouts of increased seizure activity.

Note: Phenobarbital has not been found by the FDA to be safe and effective. [11]

FDA-Approved Indications (continued)

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Carbamazepine Derivatives									
carbamazepine (Tegretol®) [12]	generic			X§	X§	X (associated with trigeminal neuralgia)			
carbamazepine extended-release (Tegretol® XR) [13]	generic								
carbamazepine extended-release (Carbatrol®) [14]	generic								
carbamazepine (Epitol®) [15]	Teva			X§	X§	X (associated with trigeminal neuralgia)			
carbamazepine (Equetro™) [16]	Validus Pharm								X
eslicarbazepine (Aptiom®) [17]	Sunovion			X*					
oxcarbazepine (Trileptal®) [18]	generic			X§					
oxcarbazepine extended-release (Oxtellar™ XR) [19]	Supernus Pharmaceuticals			X*					
Valproic Acid and Derivatives									
valproic acid (Depakene®) [20]	generic	X§	X§	X§	X§				
valproic acid delayed-release (Stavzor™) [21]	Noven Therapeutics	X§		X§	X§			X	X
divalproex delayed-release (Depakote®) [22]	generic	X§	X	X	X			X	X
divalproex sodium extended-release (Depakote ER®) [23]	generic	X§		X§				X	X

FDA-Approved Indications (continued)

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Other Anticonvulsants									
ezogabine (Potiga®) [24]	GSK			X*					
felbamate (Felbatol®) [25]	Meda			X[a§]			X*		
gabapentin (Neurontin®) [26]	generic			X*§		X (post herpetic neuralgia [PHN])			
lacosamide (Vimpat®) [27]	UCB Pharma			X*					
lamotrigine (Lamictal®, ODT) [28]	generic			X§	X*§		X*§		X
lamotrigine (Lamictal® XR) [29]	GSK			X*§	X§				
levetiracetam (Keppra™) [30]	generic		X*§	X*§	X*§				
levetiracetam XR (Keppra XR™) [31]	generic			X*§					
perampanel (Fycompa) [32]	Eisai			X§					
pregabalin (Lyrica®) [33]	Pfizer			X*		X (associated with diabetic peripheral neuropathy, spinal cord injury, or PHN)			
rufinamide (Banzel™) [34]	Eisai						X*§		
tiagabine (Gabitril®) [35]	Cephalon			X*§					
topiramate (Topamax®) [36]	generic			X§	X§		X*§	X§	
topiramate XR (Qudexy XR™) [37]	generic, Upsher-Smith			X*§	X*§		X*		
topiramate XR (Trokendi XR™) [38]	Supernus			X*§	X*§		X*		
vigabatrin (Sabril®) [39]	Lundbeck			X*§					
zonisamide (Zonegran®) [40]	generic			X*§					

[a]Felbamate (Felbatol) is not indicated as first-line antiepileptic treatment and is recommended for use only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in relation to benefits.

Other Indications: Pregabalin (Lyrica) is also indicated for treatment of fibromyalgia. Vigabatrin (Sabril) is also indicated for the treatment of infantile spasms.

OVERVIEW

Epilepsy/Seizure Disorders

Epilepsy is one of the most common disorders of the central nervous system (CNS). It affects over two million Americans, with 150,000 new cases diagnosed each year.[41] When a person has two or more seizures, they are considered to have epilepsy. Although epilepsy can develop at any age, the risk is estimated to be one percent from birth to age 20 years and three percent at age 75 years. Isolated seizures may also occur during a febrile illness, after head trauma, or as a result of withdrawal from alcohol or sedative/hypnotics.

A seizure is traceable to an unstable cell membrane or cluster of cells. Excessive excitability spreads either locally (partial seizure) or more widely (generalized seizure). Partial seizures begin in one hemisphere of the brain, and unless they become secondarily generalized, they can cause alterations in motor functioning, sensory symptoms, or automatisms. If there is no loss of consciousness, they are called simple partial. If there is loss or impairment of consciousness, they are called complex partial.

Both tonic-clonic and absence seizures are considered generalized seizures. Tonic-clonic seizures are characterized by body stiffness (tonic phase) followed by jerking movements as the muscles alternate between relaxation and rigidity (clonic phase). A tonic-clonic seizure preceded by an aura is likely a partial seizure that has secondarily generalized.

Absence seizures or petit mal seizures are more common in young children and adolescents.[42] Symptoms include staring, eye fluttering, and automatisms such as lip smacking, picking at clothes, and fumbling, if prolonged. Patients exhibit a sudden onset of lapses of awareness that begin and end abruptly, lasting only a few seconds.

Lennox-Gastaut syndrome is one of the most severe forms of childhood epilepsy and is one of the hardest forms to treat. It is characterized by mental retardation and multiple seizure types. Patients have seizures daily, sometimes experiencing several seizures within a day. Patients may also experience “drop attacks”, which is defined as a loss of muscle control causing the patient to fall abruptly to the floor.

Infantile spasm is a type of seizure seen in West Syndrome.[43] Infantile spasms primarily consist of a sudden bending forward of the body with stiffening of the arms and legs; some children arch their backs as they extend their arms and legs. West Syndrome is characterized by infantile spasms, developmental regression, and a specific pattern on electroencephalography (EEG) testing called hypsarrhythmia (chaotic brain waves). The onset of infantile spasms is usually in the first year of life, typically between four and eight months. Infantile spasms usually stop by age five, but may be replaced by other seizure types. Many underlying disorders can cause spasms, making it important to identify the underlying cause.

Goals of treating epilepsy are to reduce the frequency of seizure occurrence along with providing the best possible quality of life for the patient. Ideally, this would be achieved using a medication with minimal adverse effects and drug interactions. Treatment will depend on the type of seizure. Many different classes of drugs are available to treat the different forms of seizures.[44] Some patients will require more than one drug to control their seizures.

Standard guidelines have not been created to help differentiate the superiority of one agent over another agent. The reason for this is a lack of comparative data on which to base such a guide. This was the recurring theme in an attempt by the International League Against Epilepsy (ILAE) to develop treatment guidelines in 2013.[45] In 2004, the American Epilepsy Society (AES) and the American Academy of Neurology (AAN) developed a set of evidence-based guidelines to help healthcare professionals better understand the published research on anticonvulsant agents.[46] The guidelines summarize the use of the newer agents at the time, in patients newly diagnosed with seizures, patients with refractory seizures, and patients with refractory epilepsy. The guidelines suggest that gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), and oxcarbazepine (Trileptal) have enough supporting evidence to use as monotherapy in adolescents and adult patients newly diagnosed with partial or mixed seizures. They may also prove beneficial as adjunctive therapy in adult patients with partial seizures. Lamotrigine may be useful as monotherapy in children newly diagnosed with absence seizures. For adults and children with Lennox-Gastaut syndrome, the guidelines recommend that lamotrigine and topiramate may be used to control the "drop attacks". The guidelines mention the option of using of felbamate (Felbatol) in Lennox-Gastaut and partial seizures, but the guidelines suggest its use only when all other options have been exhausted due to the risks involved.

The American Academy of Neurology (AAN) and the Child Neurology Society recommend low-dose adrenocorticotropic hormone (ACTH) as treatment of choice for infantile spasms.[47] ACTH or vigabatrin may be useful for short-term treatment, with ACTH preferred. There is insufficient evidence that other anticonvulsants and combination therapy are effective for short-term treatment. In infants with cryptogenic infantile spasms, ACTH or prednisolone may be considered for use in preference to vigabatrin, as it may possibly result in improved developmental outcomes. A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin also possibly improves long-term developmental outcomes.

Bipolar Disorder

Bipolar disorder is characterized by episodes of mania, depression, or a mixed state. Criterion used to diagnose Bipolar I Disorder are the presence of a manic episode (persistent elevated, expansive, or irritable mood for at least one week with increased energy/activity) or a mixed features specifier (rapidly alternating polarity of mood, sadness, irritability, and mania for at least one week), and three or more other characteristic symptoms are present.[48,49] These symptoms include inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressured speech, flight of ideas or feelings of racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in risky pleasurable activities. The hallmark of a true manic episode results in symptoms severe enough to cause significant impairment in functioning, requires hospitalization to prevent harm to self or others, or the presence of psychotic features.

Criterion used to diagnose a Bipolar II Disorder includes one or more depressive episodes nearly every day during the same two-week period with at least one hypomanic episode lasting at least four days. The depressive episodes are marked by the appearance five or more depressed symptoms, which include a depressed mood most of the day every day, diminished interest in activities and hobbies, significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation nearly every day, fatigue, feeling of guilt or worthlessness, indecisiveness or inability to concentrate, and recurrent thoughts of death or suicide. Hypomanic episodes are defined as a persistently elevated, expansive, or irritable mood with increased energy/activity and three or more other symptoms. These symptoms

include inflated self-esteem, decreased need for sleep, pressured speech, distractibility, increase in goal-directed behavior, and excessive involvement with risky activities. The diagnosis of hypomania is very similar to mania, but the episodes do not result in significant impairment of functioning, they do not necessitate hospitalization, and no psychotic symptoms are present.

In 2010, the Veterans Health Administration (VHA) and the Department of Defense (DoD) published guidelines for the management of bipolar disorder in adults.[50] They recommend quetiapine, lamotrigine, or lithium monotherapy be considered as first-line treatment for adult patients with bipolar disorder depression. Combining lithium with lamotrigine can be considered for patients with bipolar disorder depression who do not respond to monotherapy. Lithium, or lamotrigine, should be considered as a first-line treatment to prevent or delay the recurrence of bipolar depression. Medications that are not recommended in patients with mania or mixed episode include topiramate, lamotrigine, and gabapentin.

Some of the anticonvulsants have been used for the treatment of bipolar disorder; a few have been approved for the treatment of bipolar disorder. Carbamazepine (Equetro), an extended-release formulation, is indicated for treatment of acute manic and mixed episodes associated with bipolar I disorder. Lamotrigine (Lamictal) is also approved for maintenance of bipolar I disorder. Several valproic acid derivatives are approved for management of bipolar disorder including valproic acid ER (Stavzor), divalproex (Depakote), and divalproex ER (Depakote ER).

Prevention of Migraine

Migraine headache prophylaxis has been suggested for patients whose headaches occur in a predictable pattern (menstrual migraine), occur more than two to three times per month, produce profound impairment, where symptomatic therapies have failed or produced serious adverse effects, and/or headaches that cannot be tolerated by the patient.[51] An evidence-based practice guideline recommended that preventive therapy goals include: reduction of migraine frequency, severity, and duration, improved responsiveness to treatment of acute attacks, improve function, and reduce disability.[52] The AAN/American Headache Society (AHS) pharmacologic treatment guidelines for episodic migraine prevention in adults recommend the following FDA-approved agents as effective treatment for migraine prevention; divalproex sodium, sodium valproate, topiramate, and the beta blockers timolol and propranolol.[53] Additional agents FDA-approved for the prevention of migraine include methysergide, and onabotulinumtoxinA (Botox®).

PHARMACOLOGY[54,55]

Drug	Mechanism of Action
Barbiturates	
primidone (Mysoline)	Barbiturates depress CNS activity by binding to the barbiturate site at the gamma-aminobutyric acid (GABA) receptor complex, enhancing GABA activity. Barbiturates reduce monosynaptic and polysynaptic transmission resulting in decreased excitability of the entire nerve cell. They also increase the threshold for electrical stimulation of the motor cortex.
phenobarbital	
Hydantoins	
ethotoin (Peganone)	The hydantoins appear to stabilize rather than raise the seizure threshold and to prevent the spread of seizure activity rather than abolish the primary focus of discharge. The primary site of action appears to be the motor cortex. Possibly by promoting sodium efflux from neurons, hydantoins tend to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient.
Phenytoin (Dilantin, Phenytek)	
Succinimides	
ethosuximide (Zarontin)	Succinimides suppress the paroxysmal three-cycles-per-second spike and wave activity associated with lapses of consciousness common in absence seizures. The frequency of epileptiform attacks is reduced, apparently by motor cortex depression and elevation of the threshold of the CNS to convulsive stimuli.
methsuximide (Celontin)	
Benzodiazepines	
clobazam (Onfi)	Benzodiazepines potentiate the effects of GABA. Benzodiazepines suppress the spike and wave discharge associated with absence seizures.
clonazepam (Klonopin)	
diazepam rectal gel (Diastat)	
Carbamazepine Derivatives	
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)	Carbamazepine reduces polysynaptic responses and blocks the post-tetanic potentiation. The mechanism of action of carbamazepine in bipolar disorder and treatment of pain in trigeminal neuralgia is unknown.
eslicarbazepine acetate (Aptiom)	Eslicarbazepine is a voltage-gated sodium channel (VGSC) blocker. Eslicarbazepine and its metabolites competitively interact with site two of the inactivated state of VGSC, inhibiting sustained repetitive neuronal firing. Eslicarbazepine has a much higher affinity for the inactivated state of VGSC than the resting state, suggesting an enhanced inhibitory selectivity for rapidly firing neurons over those displaying normal activity.
oxcarbazepine (Trileptal, Oxtellar XR)	*In vitro* electrophysiological studies indicate that oxcarbazepine produces blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses.

Pharmacology (continued)

Drug	Mechanism of Action
Valproic Acid And Derivatives	
valproic acid (Depakene) valproic acid ER (Stavzor) divalproex (Depakote, Depakote ER, Depakote Sprinkle)	Valproic acid and derivatives increase brain concentration of GABA.
Other Anticonvulsants	
felbamate (Felbatol)	*In vitro* studies indicate felbamate has weak inhibitory effects on GABA-receptor binding and benzodiazepine receptor binding.
ezogabine (Potiga)	In vitro studies indicate that ezogabine enhances transmembrane potassium currents which are thought to stabilize the resting membrane potential and reduce brain excitability. In vitro data suggest that augmentation of GABA-mediated currents may also contribute to the therapeutic effects of ezogabine.
gabapentin (Neurontin)	Gabapentin binds to the presynaptic α_2-delta subunit of voltage sensitive calcium channels.
lacosamide (Vimpat)	Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.
lamotrigine (Lamictal, Lamictal XR)	Lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes which modulate presynaptic transmitter release of excitatory amino acids.
levetiracetam (Keppra, Keppra XR)	Levetiracetam inhibits burst firing without affecting normal neuronal excitability. It may also prevent propagation of seizure activity.
perampanel (Fycompa)	Perampanel is a non-competitive antagonist of the ionotropic AMPA glutamate receptor on postsynaptic neurons.
pregabalin (Lyrica)	Pregabalin binds to presynaptic α_2-delta subunit of voltage sensitive calcium channels, inhibiting release of pro-nociceptive neurotransmitters in the spinal cord
rufinamide (Banzel)	*In vitro* studies indicate rufinamide modulates the activity of the sodium channels by prolonging the inactivity of the channel.
tiagabine (Gabitril)	Tiagabine enhances the activity of GABA.
topiramate (Topamax, Qudexy XR, Trokendi XR)	Topiramate exhibits sodium channel blocking action; potentiates activity of GABA; antagonizes the glutamate (excitatory amino acid) receptor; and inhibits carbonic anhydrase.
vigabatrin (Sabril)	Vigabatrin is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the CNS.
zonisamide (Zonegran)	Zonisamide blocks sodium channels and reduces voltage-dependent, transient, inward currents, consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. It also facilitates both dopaminergic and serotonergic transmission and is a weak carbonic anhydrase inhibitor.

PHARMACOKINETICS

Drug	Half-Life (Hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (µG/mL)
Barbiturates				
primidone (Mysoline)[56]	10-12	PEMA (half-life 29-36 hours) phenobarbital (half-life 53-140 hours)	Renal: 64	5-12 15-40
phenobarbital[57]	53-140	--	Urine: 25	15-40
Hydantoins				
ethotoin (Peganone)[58]	3-9	3	Metabolites-Urine	15-50
phenytoin (Dilantin, Phenytek)[59, 60]	7-42	No	After reabsorption from intestinal track- Urine	10-20
Succinimides				
ethosuximide (Zarontin)[61]	60 (adults) 30 (children)	No	Parent unchanged 12-20 metabolites 40-60 Renal	40-100
methsuximide (Celontin)[62]	2.6-4	N-desmethyl-methsuximide (NDM)	--	--
Benzodiazepines				
clobazam (Onfi)[63]	36-42	N-desmethylclobazam (half-life 71-82 hours)	Urine: 2 Feces: 1	--
clonazepam (Klonopin)[64]	30-40	No	Metabolites Urine	20-80 ng/mL
diazepam rectal gel (Diastat)[65]	46	desmethyldiazepam (half-life 71 hours) 3-hydroxydiazepam 3-hydroxy-N-diazepam	Metabolites Urine	--
Carbamazepine Derivatives				
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)[66, 67, 68 69]	25-65 initially then 12-17 after repeated doses	10,11-epoxide	Metabolites Urine: 72 Feces: 28	4-12
eslicarbazepine acetate (Aptiom)[70]	13-20	eslicarbazepine	Renal: 60 Metabolites Urine: 40	--

Pharmacokinetics (continued)

Drug	Half-Life (Hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (mcg/mL)
Carbamazepine Derivatives				
oxcarbazepine (Trileptal)[71]	2	10-mono-hydroxy (MHD, half-life 9 hours)	Metabolites Urine: 95 Feces: <4	--
oxcarbazepine (Oxtellar XR)*[72]	7-11	10-mono-hydroxy (MHD, half-life 9 hours)	Metabolites Urine: 95 Feces: <4	--
Valproic Acid And Derivatives				
valproic acid (Depakene)[73], valproic acid ER (Stavzor)[74], divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)[75, 76]	9-16	Yes	Metabolites Renal	50-100
Other Anticonvulsants				
ezogabine (Potiga)[77]	7-11	N-acetyl metabolite of ezogabine (NAMR)	Urine: 85 (36 unchanged) Feces:14	--
felbamate (Felbatol)[78]	20–23	No	Metabolites Urine: >90	--
gabapentin (Neurontin)[79]	5–7	No	Renal	--
lacosamide (Vimpat)[80]	13	No	Urine: 95	--
lamotrigine (Lamictal)[81]	25	No	Urine: 94 Feces: 2	--
lamotrigine (Lamictal XR)[82]	33	No	Urine: 94 Feces: 2	--
levetiracetam (Keppra, Keppra XR)[83, 84]	6–8	No	Urine: 66 unchanged	--
perampanel (Fycompa)[85]	105	No	Urine: 22 Feces: 48	--
pregabalin (Lyrica)[86]	6	No	Urine: 90-98 unchanged	--
rufinamide (Banzel)[87]	6–10	No	Urine: 85	--
tiagabine (Gabitril)[88]	7–9	No	Metabolites Urine: 25 Metabolites Feces: 63	--

Pharmacokinetics (continued)

Drug	Half-Life (Hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (mcg/mL)
Other Anticonvulsants *(continued)*				
topiramate (Topamax®) [89]	21	No	Urine: (70 unchanged)	--
topiramate XR (Qudexy™ XR) [90]	56	No	Urine: (70 unchanged)	--
topiramate XR (Trokendi XR™) [91]	31	No	Urine: (70 unchanged)	--
vigabatrin (Sabril) [92]	7.5	No	Urine 95 (80 unchanged)	--
zonisamide (Zonegran) [93]	63	N-acetyl zonisamide SMAP	Urine: 62 (35 unchanged) Feces: 3	--

*At steady state, oxcarbazepine ER (Oxtellar XR) once daily produced MHD exposures (AUC and Cmax) about 19 percent lower and MHD minimum concentrations (Cmin) about 16 percent lower than IR oxcarbazepine administered at the same 1,200 mg total daily dose. When oxcarbazepine ER was administered at an equivalent 600 mg single dose equivalent MHD exposures (AUC) were observed.

CONTRAINDICATIONS/WARNINGS

Drug	Selected Warnings	Monitoring
barbiturates [94]	habit forming, additive CNS depression when used with other CNS depressants, contraindicated in patients with porphyria, marked impairment of liver function, or respiratory disease in which dyspnea or obstruction is evident.	periodic lab evaluation of hematopoietic, hepatic, and renal systems
benzodiazepines [95, 96, 97]	interference with cognitive and motor functioning	periodic blood counts and liver function tests (LFTs)
carbamazepines [98, 99, 100 101]	serious dermatologic reactions (e.g. Steven Johnsons Syndrome, especially in Han Chinese (25%) and significant levels in other southeast Asians with high proportion of Han Chinese ancestry (e.g. Bangkok Thai), bone marrow suppression	testing for HLA-B*1502 in patients with Asian ancestry, pretreatment blood count
hydantoins [102, 103, 104]	lymphadenopathy, alcohol intake, exacerbation of porphyria, hepatic abnormalities and hematologic disorders	serum concentrations, complete blood count (CBC), LFTs, urinalysis
succinimides [105, 106]	blood dyscrasias, functional liver and renal changes, systemic lupus erythematosus (SLE)	periodic blood counts, liver function testing, urinalysis

In 2008, the Food and Drug Administration (FDA) informed healthcare professionals that the Agency has analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of eleven drugs used to treat epilepsy, as well as psychiatric disorders and other conditions.[107] In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal

behavior or ideation (0.43 percent) compared to patients receiving placebo (0.22 percent). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the eleven drugs. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions.

Healthcare professionals should closely monitor all patients currently taking or starting any antiepileptic drug for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts, behavior, or depression. The 11 drugs included in the analysis were carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol XR), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax, Qudexy XR, Trokendi XR), valproate (Depakote, Depakote ER, Depakene, Stavzor), and zonisamide (Zonegran). Even though other products were not included in the analysis, the risk of suicidal behavior and suicidal ideation is still possible and should be monitored in patients receiving treatment. All antiepileptic drugs contain this warning.

All antiepileptic drugs should be gradually withdrawn to minimize the potential of increased seizure frequency.

In pregnancy, the use of anticonvulsants is associated with congenital malformations including craniofacial anomalies, neurological abnormalities, and congenital heart defects.[108] An observational study from the United Kingdom Epilepsy and Pregnancy Registry of 3,607 females identified the rate of congenital malformations in women using all epileptics was 4.2 percent versus 3.5 percent with untreated epilepsy. The risk was higher in those women that used polytherapy six percent versus monotherapy 3.7 percent. Several studies have suggested that the use of valproate may have a higher risk compared to other antiepileptics.[109, 110, 111]

Benzodiazepines should not be used in patients with clinical or biochemical evidence of significant liver disease. They may be used in patients with open angle glaucoma who are receiving appropriate therapy but are contraindicated in acute narrow angle glaucoma.

clobazam (Onfi)[112]

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults. Patients should be closely monitored for signs or symptoms especially during the first eight weeks of treatment or when re-introducing therapy.

Somnolence or sedation associated with clobazam is dose related and reported in all effective doses but may abate after the first month of treatment. Patients should limit activities that require mental alertness until the effect of the mediation is known. Additional CNS depressants, including other medications and alcohol, may increase sedative side effects.

Tapering a benzodiazepine should occur slowly to avoid withdrawal symptoms. Withdrawal symptoms include seizure exacerbation, status epilepticus, psychosis, hallucinations, tremor, anxiety, and behavioral disorders. To minimize the risk, tapering should occur by decreasing 5-10 mg/day every week until discontinued. More severe withdrawal symptoms are experience by patients using higher doses or taking therapeutic doses for longer periods of time. Similar to other benzodiazepines patients may become physically and psychological dependent on clobazam, and patients with substance abuse history should be closely monitored.

carbamazepine (Carbatrol, Equetro, Tegretol/XR, Epitol)[113,114,115,116]

For carbamazepine products, serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to occur in one to six per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about ten times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS or TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

There is a moderate association between the risk of developing hypersensitivity reactions, including SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and the presence of HLAA*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. HLA-A*3101 is carried by more than 15 percent of Japanese, Native American, Southern Indian, and some Arab patients; up to about 10 percent of Han Chinese, Korean, European, Latin American, and other Indian patients ancestry; and up to about five percent in African-Americans and patients of Thai, Taiwanese, and Chinese ancestry.

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data from a population-based, case-control study indicates the risk of developing these reactions is five to eight times greater than in the general population; however, the overall risk of developing these reactions in the untreated general population is low. Furthermore, these reactions occur in approximately six patients per one million population per year for agranulocytosis, and two patients per one million populations per year for aplastic anemia. Even though reports of transient or persistent decreased platelet or white blood cell counts are associated with the use of carbamazepine, data are not available to accurately estimate their incidence or outcome. The majority of the reported cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis. Due to the very low incidence of agranulocytosis and aplastic anemia, the majority of minor hematologic changes observed while monitoring patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing at baseline should be obtained, and monitoring should occur if the patient exhibits low or decreased white blood cell or platelet counts during treatment. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline. Theoretically, the use of carbamazepine with monoamine oxidase (MAO) inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days or longer if the clinical situation permits. Carbamazepine should be avoided in patients with a history of hepatic porphyria (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). Acute attacks have been reported in such patients receiving carbamazepine therapy.

Rare instances of vanishing bile duct syndrome have been reported with carbamazepine. This syndrome consists of a cholestatic process with a variable clinical course ranging from fulminant to

indolent, involving the destruction and disappearance of the intrahepatic bile ducts. Some cases are associated with features of other immunoallergenic syndromes such as multiorgan hypersensitivity (DRESS syndrome) and serious dermatologic reactions, including Stevens-Johnson syndrome.

eslicarbazepine acetate (Aptiom)[117]

Eslicarbazepine acetate is contraindicated in patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.

Serious dermatologic reactions including SJS have been reported with eslicarbazepine acetate. Both SJS and TEN have been reported in patients using oxcarbazepine or carbamazepine, which are chemically related to eslicarbazepine acetate. Patients with a prior dermatologic reaction with oxcarbazepine should not be treated with eslicarbazepine acetate.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported with eslicarbazepine acetate and may be fatal or life-threatening. If evidence of hypersensitivity presents, the patient should be evaluated immediately, the product discontinued, and not resumed if an alternative etiology cannot be established. Patients with a prior DRESS reaction with either oxcarbazepine or eslicarbazepine acetate should not be treated with eslicarbazepine acetate.

Hyponatremia can develop in patients on eslicarbazepine acetate. It is generally dose-related and usually appears in the first eight weeks of treatment. Sodium and chloride levels should be monitored throughout treatment. Neurological adverse reactions including dizziness, changes in coordination, somnolence, cognitive dysfunction, visual changes, and fatigue have been noted.

Eslicarbazepine acetate also causes dose-dependent increases in visual changes including diplopia, and blurred, and impaired vision. This is more common in patients older than 60 years of age or when used concomitantly with carbamazepine. There may also be dose-dependent increases in somnolence and fatigue-related adverse reactions as well as cognitive dysfunction. Patients should not engage in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effects of eslicarbazepine acetate are known.

Elevations in transaminases (greater than three times the upper limit of normal) with concomitant elevations of total bilirubin (greater than two times the upper limit of normal) without obstruction have been reported with eslicarbazepine acetate. Baseline and periodic liver laboratory tests are recommended.

ezogabine (Potiga)[118]

Ezogabine carries a boxed warning regarding retinal pigmentary abnormalities with long-term use. Patients who fail to show substantial clinical benefit after adequate titration should be discontinued from ezogabine. Approximately one third of the patients who had eye examinations performed after approximately four years of treatment were found to have retinal pigmentary abnormalities – although an earlier onset cannot be ruled out. The rate of progression of retinal abnormalities and their reversibility are currently unknown. Testing of visual function should be done at baseline and every six months during therapy with ezogabine. Patients who cannot be monitored should usually not be treated with ezogabine. If retinal pigmentary abnormalities or vision changes are detected, ezogabine should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.

Ezogabine can cause a blue skin discoloration, although it has also been described as grey-blue or brown. It is predominantly on or around the lips or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs has also been reported. Approximately 10 percent of patients in long-term trials developed skin discoloration, generally after two or more years of treatment and at higher doses (900 mg or greater) of ezogabine. Many of these subjects also had concurrent retinal pigmentary abnormalities. If a patient develops skin discoloration, serious consideration should be given to changing to an alternate medication.

During clinical trials, psychiatric symptoms including confusional state, psychotic symptoms, and hallucinations occurred more frequently in patients receiving ezogabine than placebo. Half of the patients in clinical trials who discontinued ezogabine due to hallucinations or psychosis required hospitalization, and two-thirds of patients with psychosis in clinical trials had no prior psychiatric history.

A study of cardiac conduction showed QT prolongation occurring in healthy volunteers during administration of ezogabine. The QT interval should be monitored in patients with known QT prolongation, congestive heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesaemia. The QT interval should also be monitored in patients receiving medications known to cause QT prolongation.

felbamate (Felbatol)[119]

Felbamate is not indicated as a first line antiepileptic therapy. It is recommended for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that the benefits of its use outweighs the substantial risk of aplastic anemia and/or liver failure conferred by its use. Among felbamate-treated patients, aplastic anemia occurs at an incidence of more than 100-fold greater than that seen in the untreated population. The clinical manifestation of aplastic anemia may not be seen until after a patient has been on felbamate for several months; however, the injury to the bone marrow stem cells that is ultimately responsible for the anemia may occur weeks to months earlier. Patients who discontinue felbamate remain at risk for developing anemia for a variable and unknown period afterwards. Felbamate should be discontinued if bone marrow suppression develops. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but in some cases, it will allow for the detection of hematologic changes before the syndrome presents clinically.

Post marketing data suggests that acute liver failure is associated with the use of felbamate. Of the reported cases, two-thirds resulted in death or liver transplantation, usually within five weeks of the onset of signs and symptoms of liver failure. Felbamate should be initiated only in patients without active liver disease and with normal baseline serum transaminases. Periodic serum transaminase testing may detect early drug-induced hepatic injury, but it has not been proven to prevent serious injury. Immediate withdrawal of felbamate is warranted with evidence of hepatic injury (≥ two times upper limit of normal for aspartate aminotransferase [AST] or alanine aminotransferase [ALT] or if clinical signs and symptoms develop). Baseline and periodic monitoring of serum transaminases (AST and ALT) are recommended. Patients are considered at an increased risk of liver injury if felbamate is reintroduced after the development of hepatocellular injury during felbamate treatment and who are withdrawn from the drug for any reason. These patients should not return to felbamate treatment. Treatment with felbamate should occur only if the criteria for normal liver function are met, the patient has been fully advised of the risk, and has provided written, informed consent. After meeting these recommendations, it can be considered for either monotherapy or adjunctive therapy in adults.

lacosamide (Vimpat)[120]

Dose-dependent PR interval prolongation and atrioventricular block have been observed in clinical trials. Lacosamide should be used with caution in patients with known cardiac conduction problems or with severe cardiac disease such as myocardial ischemia or heart failure. Atrial fibrillation and flutter have also been reported.

lamotrigine (Lamictal, Lamictal XR)[121, 122]

Serious rashes including Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine. The incidence of these rashes, which have included SJS, is approximately 0.8 percent in pediatric patients (age <16 years) and 0.3 percent in adults receiving lamotrigine as adjunctive therapy for epilepsy. Based on the labeling, the rates in children appear to be correlated with the rapid dose escalations, surpassing FDA recommended dose, and concomitant use with valproate. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08 percent in adult patients receiving lamotrigine as initial monotherapy and 0.13 percent receiving as adjunctive therapy. Rare cases of TEN and/or rash-related death have been reported in adult and pediatric patients. Although uncertain, the coadministration of lamotrigine with valproate, exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine may increase the risk of rash; however, case reports have occurred in the absence of these factors. Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within two to eight weeks after treatment initiation. Benign rashes also occur with lamotrigine; however, it is difficult to determine which rashes will prove serious or life-threatening. Recommendations are to discontinue lamotrigine at the first sign of rash unless the rash is clearly not drug-related.

Aseptic meningitis has been reported in both children and adults receiving lamotrigine. The FDA identified 40 cases of aseptic meningitis in patients receiving lamotrigine from December 1994 to November 2009. Post-marketing reports indicate that symptoms may include headache, fever, nausea, vomiting, and nuchal rigidity, as well as rash, photophobia, myalgia, chills, altered consciousness, and somnolence. Cerebrospinal fluid analysis has shown mild to moderate pleocytosis, normal glucose concentrations, and mild to moderate increases in protein. Some patients have had an underlying autoimmune disease such as systemic lupus erythematosus (SLE). New onset hepatic and renal involvement have occurred in some instances, which may suggest these cases were part of a hypersensitivity reaction. Aseptic meningitis associated with lamotrigine has historically developed between one day and 1.5 months after treatment initiation, and resolution usually occurs upon discontinuation of the drug. Re-exposure to lamotrigine can result in a rapid return of the condition (e.g., 30 minutes to one day) with more severe symptoms. If aseptic meningitis is suspected during the use of lamotrigine, the patient should be promptly evaluated and the underlying cause diagnosed so that the appropriate treatment can be initiated. Discontinuation of lamotrigine should be considered if no other cause can be identified. Patients receiving lamotrigine should be advised to report signs and symptoms of meningitis to their healthcare professional.[123]

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a multi-organ hypersensitivity reaction, has occurred with lamotrigine. Manifestations of DRESS typically include fever, rash, and/or lymphadenopathy in conjunction with other organ system abnormalities including hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis. Eosinophilia is often present. Early manifestations such as fever and lymphadenopathy may be present without evidence of a rash. Cases of isolated

hepatic failure without rash or other organ involvement have also been reported. Three cases of multiorgan dysfunction and disseminated intravascular coagulation (DIC) occurred within 14 days of adding lamotrigine to an existing antiepileptic drug regimen, with subsequent resolution of symptoms following discontinuation of the drug. Fatalities associated with hepatic failure or multiorgan failure occurred in two of 3,796 adults and four of 2,435 pediatric patients during clinical trials. Fatalities have also been reported rarely during post-marketing use. Pruritus was reported in two percent of pediatric patients and five percent or more of adult patients during clinical trials. Maculopapular rash and urticaria were reported infrequently (0.1-one percent). Angioedema, erythema, and eosinophilia occurred rarely (< 0.1 percent).[124,125]

levetiracetam (Keppra, Keppra XR)[126,127]

In adults experiencing partial onset seizures, levetiracetam is associated with the occurrence of CNS adverse events that can be classified into the categories of somnolence and fatigue, coordination difficulties, and behavioral abnormalities. Somnolence, asthenia, and coordination difficulties occur most frequently within the first four weeks of treatment. Also, levetiracetam is associated with somnolence, fatigue, and behavioral abnormalities in pediatric patients experiencing partial onset seizures. Psychiatric abnormalities also occurred in adult studies in generalized tonic-clonic seizures and pediatric studies in partial onset seizures. Behavioral abnormalities include both psychotic and non-psychotic reactions. There is a worsening of aggressive behavior in children with 11.7 percent of children from one month to less than four years of age exhibiting irritability. Psychosis developed in one percent of adults, two percent of children four to 16 years of age, and 17 percent of children one month to less than four years of age.

Severe dermatological reactions, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), has been reported in children and adults treated with levetiracetam. Usual onset is 14-17 days after initial treatment, but cases have been reported for patients using the medications for 16 weeks. The medication should be discontinued at the first sign of a rash, unless it can be definitively established that the rash is not due to the medication. Medication trials are not recommended after resolution of possible SJS or TEN.

oxcarbazepine/ER (Trileptal, Oxtellar XR)[128,129]

Clinically significant hyponatremia, defined as serum sodium level less than 125 mmol/L, can develop during oxcarbazepine use and has generally occurred during the first three months of treatment. Some patients first developed hyponatremia more than one year after initiation of therapy, which highlights the importance of monitoring serum sodium levels during maintenance treatment with oxcarbazepine. Monitoring should occur, especially if the patient is receiving other medications known to decrease serum sodium levels, such as those associated with inappropriate antidiuretic hormone secretion or if symptoms develop that possibly indicate hyponatremia, such as lethargy, confusion, obtundation, or increase in seizure frequency or severity.

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids in patients after taking the first or subsequent doses of immediate-release (IR) oxcarbazepine have been reported. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with oxcarbazepine IR or ER, the drug should be discontinued and an alternative treatment started. These patients should not be rechallenged with the drug.

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25 to 30 percent of them will experience hypersensitivity reactions with oxcarbazepine. For this reason, a thorough history of hypersensitivity reactions with carbamazepine should be obtained prior to treatment, and patients with a positive history should receive oxcarbazepine only if the potential benefit justifies the potential risk.

Serious dermatological reactions, including SJS and TEN, have been reported in both children and adults in association with oxcarbazepine use. The median time of onset for reported cases was 19 days. The presence of the HLA-B*1502 allele may put patients at an increased risk for SJS and TEN development. The risk of using oxcarbazepine in patients who carry the HLA-B*1502 allele should be carefully compared to the potential benefit.

perampanel (Fycompa)[130]

Perampanel carries a black box warning for serious psychiatric and behavioral reactions. Patients taking perampanel also exhibited an increased risk of hostile and aggressive related behavior during Phase III clinical trials occurring at a greater rate than patients receiving placebo. These effects were dose-related and typically emerged in the initial six weeks of therapy although new events were seen to emerge through more than 37 weeks of therapy. Events included irritability, anger, aggression, and anxiety and were seen twice as often in the treatment group as compared to the placebo group. Additional issues including belligerence, affect liability, agitation, and physical assault were seen with some and reported as serious and/or life threatening. The events listed were seen in patients with and without a prior history of such behavior, psychiatric history, or use of other medications noted to cause hostility and aggression. Patients, caregivers and their families should be instructed of the potential increased risk of psychiatric events with use of perampanel. Patients should additionally be monitored for changes in behavior or mental status during treatment, particularly with higher doses and during titration. Monitoring should be continued for one month after the cessation of therapy. If any of the noted problems do occur, dosage should be reduced and subsequently discontinued if symptoms persist or worsen with patients being referred for a complete psychiatric evaluation.

The use of perampanel may increase the risk of suicidal thoughts or behavior in patients and the potential risk versus benefit should be considered. Patients receiving treatment with perampanel should be closely monitored for any signs of worsening depression, suicidal thoughts or behaviors, and/or changes in mood or behavior.

Perampanel may also cause certain neurologic effects including gait disturbances, dizziness, and somnolence. These effects generally occurred during the titration phase and were dose-dependent. Patients should be advised against engaging in potentially hazardous activities until the possible effects of perampanel use are determined.

In clinical trials, perampanel use showed an increased fall risk that resulted, in some cases, in head injuries along with bone fracture injuries. During Phase III trials, patients randomized to 8 mg and 12 mg per day dosing reported falls in five percent and 10 percent of patients compared to those receiving placebo where falls were seen in three percent of patients. These falls, reported as serious, resulted in more frequent discontinuation by perampanel patients than patients treated with placebo. Elderly patients in the trials were at a greater risk of experiencing falls compared to younger adults and adolescents.

As with other antiepileptic drugs (AEDs), perampanel, should be withdrawn slowly to minimize the potential for increased seizure activity except in cases where the withdrawal is in response to severe adverse events.

The concomitant use of perampanel and CNS depressants including alcohol may increase CNS depressant effect.

phenytoin (Dilantin, Phenytek)[131, 132]

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness (e.g., fever, rash, and liver involvement). In all cases of lymphadenopathy, follow-up observation for an extended period is indicated, and every effort should be made to achieve seizure control using alternative antiepileptic drugs. Acute alcoholic intake may increase phenytoin serum levels, while chronic alcohol use may decrease serum levels. Phenytoin is contraindicated in those patients with a history of hypersensitivity to phenytoin or other hydantoins, as well as in combination with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine and other non-nucleoside reverse transcriptase inhibitors.

Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported with phenytoin treatment. If a rash occurs, the patient should be evaluated for signs and symptoms of drug reaction with Eosinophilia and Systemic Symptoms. The presence of HLA-B*1502, in patients of Chinese ancestry may be a risk factor for the development of SJS/TEN with phenytoin and other antiepileptic drugs associated with SJS/TEN.

primidone (Mysoline)[133]

Primidone is contraindicated in patients with porphyria and patients who are hypersensitive to phenobarbital.

rufinamide (Banzel)[134]

Rufinamide demonstrated a decrease in the QT interval and is contraindicated in patients with familial short QT syndrome. Patients with this syndrome have an increased risk of sudden death and ventricular arrhythmias. It should also be used with caution in patients already receiving drugs that shorten the QT interval.

During clinical trials, patients less than 12 years of age receiving rufinamide for at least four weeks experienced multi-organ hypersensitivity syndrome. The patients presented with a rash and at least one of the following symptoms: fever, elevated liver function tests, hematuria, and lymphadenopathy; however, due to the variability in the syndrome's expression, abnormalities in other organ systems may indicate the presence of this syndrome. If this syndrome is suspected, rufinamide should be discontinued, and an alternative therapy started. Also, patients who develop a rash without any other symptoms during treatment should be closely monitored.

To prevent the precipitation of seizures, seizure exacerbation, or status epilepticus during discontinuation, rufinamide should be gradually withdrawn by decreasing the dose by approximately

25 percent every two days. Patients who require abrupt discontinuation due to medical necessity should be closely monitored while being transitioned over to another agent.

topiramate (Qudexy XR, Topamax, Trokendi XR)[135, 136, 137]

Hyperchloremic, non-anion gap, metabolic acidosis (e.g., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment especially in children under two years of age with partial onset seizures. Metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may add to the bicarbonate lowering effects of topiramate. Qudexy XR is contraindicated in patients with metabolic acidosis who are also taking concomitant metformin.[138]

Oligohidrosis with topiramate, resulting in elevated body temperatures especially with exposure to elevated environmental temperatures has resulted in hospitalization, especially in pediatric patients.

Topiramate has produced hyperammonemia (in some instances dose-related), in clinical studies in children and postmarketing, and has occurred with and without encephalopathy. Symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used concomitantly with valproic acid and may occur in patients who previously tolerated either drug alone. Although hyperammonemia with and without encephalopathy has been observed in patients who were taking topiramate alone without concomitant valproic acid. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk.

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within one month of initiating topiramate. Topiramate should be discontinued.

Visual field defects have been reported with topiramate independent of elevated intraocular pressure. If visual problems occur consideration should be given to discontinuing the drug.

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring.

Trokendi XR is contraindicated in patients who have consumed alcohol within six hours before and/or after the dose due to a significant alteration in topiramate release from the Trokendi XR capsules. In the presence of alcohol, topiramate plasma levels may be markedly higher soon after the dose and subtherapeutic the next day.

valproate/divalproex (Depakene, Depakote/ER, Stavzor)[139,140,141,142]

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of two years are at increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When valproic acid/divalproex is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

Valproate derivatives can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of valproic acid/divalproex in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus.

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate and its derivatives. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should be discontinued.

Valproate/divalproex products are contraindicated in patients with hepatic disease or significant hepatic dysfunction, known hypersensitivity to the drug, urea cycle disorders, or for use as migraine prophylaxis in pregnant women.

Valproate/divalproex products are also contraindicated in patients with mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder.

vigabatrin (Sabril)[143]

Vigabatrin can cause irreversible vision loss. Because of this, if clinical improvement is not seen within two to four weeks of treatment, vigabatrin should be discontinued. Vision testing should be administered at baseline, at least every three months while on therapy, and about three to six months after discontinuation.

Due to the irreversible vision loss, vigabatrin is available only under a special restricted distribution program called SHARE. Under SHARE, only prescribers and pharmacies registered with the program are able to prescribe and distribute vigabatrin, and it may be dispensed only to patients who are enrolled in and meet all conditions.

Patients may be exempted from vision assessment under limited conditions, including patient blindness or when the patient's general neurological and/or mental condition permanently precludes the need for visual assessment. Abnormal MRI signal changes and vacuolization have also been reported with vigabatrin use.

zonisamide (Zonegran)[144]

Zonisamide is contraindicated in patients with hypersensitivity to sulfonamides. Zonisamide may cause a severe rash, including Stevens-Johnson syndrome, and toxic epidermal necrolysis. Patients who develop a rash should stop taking zonisamide. Hepatic necrosis, agranulocytosis, and aplastic anemia have also resulted from hypersensitivity. Oligohidrosis, hyperthermia, metabolic acidosis, and heat stroke are also reported in patients on zonisamide. Pediatric patients appear to be at a greater risk.

Medication Guide/Risk Mitigation Evaluation Strategy (REMS)

These products must be dispensed with a Medication Guide: carbamazepine (Equetro), clonazepam (Klonopin), ethotoin (Peganone), ethosuximide (Zarontin), ezogabine (Potiga), gabapentin (Neurontin), lacosamide, lamotrigine (Lamictal, Lamictal ODT, Lamictal XR), levetiracetam (Keppra, Keppra XR), methsuximide (Celontin), oxcarbazepine (Trileptal, Oxtellar XR), pregabalin, rufinamide, tiagabine, topiramate (Qudexy XR, Topamax, Trokendi XR), and zonisamide.

In addition to a Medication Guide, vigabatrin is associated with a Communication Plan that will send Dear Healthcare Professional Letters to all registered ophthalmologists annually. An Implementation System requires that the manufacturer maintain a database of certified pharmacies and prescribers and enrolled patients. The manufacturer must also ensure proper training of all parties involved with the proper dispensing of vigabatrin. Elements to assure safe use mandate that healthcare providers and dispensing pharmacies issuing vigabatrin prescriptions be certified, and that vigabatrin is dispensed to recipients who meet treatment criteria and are registered properly. Vision assessments should be performed at initiation, every three months during therapy, and about three to six months after discontinuation.

DRUG INTERACTIONS

There are many different drug interactions associated with each anticonvulsant agent. Phenobarbital, phenytoin (Dilantin, Phenytek), primidone (Mysoline), and carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro, Epitol) are potent inducers of CYP 450 and other enzyme systems.

Barbiturates can induce hepatic microsomal enzymes resulting in increased metabolism and decreased anticoagulant response in oral anticoagulants (e.g., warfarin, acenocoumarol, dicoumarol and phenprocoumon). Phenobarbital has been shown to shorten the half-life of doxycycline for as long as 2 weeks after barbiturate therapy is discontinued. MAO inhibitors prolong the effects of barbiturates probably because metabolism of the barbiturate is inhibited.

Ethosuximide (Zarontin) is metabolized mainly by CYP 3A4 enzyme via hydroxylation to inactive metabolites.[145] Drugs that inhibit, induce, or are metabolized by this enzyme can change the therapeutic levels of the active drug. Depending on the type of drug interaction, dosages of ethosuximide or the interacting drug may need to be adjusted and monitored. Ethosuximide does not inhibit or induce CYP 450 isozymes. Lacosamide (Vimpat) is a CYP 2C9, 2C19, and 3A4 substrate, but it does not induce or inhibit CYP enzymes. Vigabatrin (Sabril) may induce CYP 2C enzymes in some patients. Methsuximide may increase the plasma concentrations of phenytoin and phenobarbital.

The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, anti-anxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated. Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity. Concomitant medication with carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia. Carbamazepine may antagonize the effects of nondepolarizing muscle relaxants (e.g., pancuronium). Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.[146, 147, 148, 149]

Eslicarbazepine acetate (Aptiom) can inhibit CYP2C19 and can elevate concentrations of phenytoin or other drugs metabolized by CYP2C19.[150] *In vivo* studies suggest that it can induce CYP3A4, decreasing plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., simvastatin) and several antiepileptics (e.g., carbamazepine, phenobarbital, phenytoin, and primidone) can induce enzymes that metabolize eslicarbazepine acetate and can cause decreased plasma concentrations. Perampanel (Fycompa) is both a substrate and weak inducer of CYP3A4/5.[151] Perampanel concentrations may be decreased by up to 50 to 67 percent, when used concomitantly with cytochrome (CYP) P450 enzyme inducers including phenytoin, oxcarbazepine or carbamazepine and starting doses should be increased when used with such inducers.

Rufinamide (Banzel) is a weak inducer of the CYP 3A4 enzyme and has been shown to cause a decrease concentration of drugs that are substrates of the CYP 3A4 enzyme.[152] It is also a weak inhibitor of CYP 2E1. Drugs that induce carboxylesterases, such as carbamazepine and phenobarbital, may decrease the concentration of rufinamide; while drugs that inhibit the carboxylesterase enzymes may increase the concentration of rufinamide. Rufinamide has been shown to increase the plasma concentration of phenytoin by 21 percent or more, and valproic acid (Depakene) has been shown to increase the concentration of rufinamide up to 70 percent.

The concomitant use of topiramate (Qudexy XR, Topamax, Trokendi XR) with any other drug producing metabolic acidosis (e.g., zonisamide, acetazolamide, or dichlorphenamide), or potentially in patients on a ketogenic diet, may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. The use of metformin is contraindicated in metabolic acidosis conditions.

Use of topiramate (Qudexy XR, Topamax, Trokendi XR) and valproic acid (VPA) concurrently can result in hypothermia with or without hyperammonemia. Hypothermia is defined as a drop in core body temperature <35°C (95°F). Hypothermia can present with a variety of symptoms that include lethargy, confusion, coma, and shifts in other major organ systems including cardiovascular and respiratory systems. Clinical management should include stopping one of the medications and evaluation of ammonia levels.

Zonisamide (Zonegran) is principally inactivated by CYP 3A4-dependent reduction; therefore, when used in combination with CYP3A4 inducers, its clearance is increased resulting in the possible necessity of a dosage increase.[153] Valproate derivatives (Depakene, Depakote/ER, Stavzor) inhibit many hepatic enzyme systems and can displace drugs from albumin.

Carbamazepine (40 to 90 percent), phenytoin (90 percent), primidone (80 percent), tiagabine (Gabitril) (95 percent), and valproic acid (80 to 95 percent) are highly bound to protein. Tiagabine is displaced

from protein by naproxen, salicylates, and valproic acid. Valproic acid displaces diazepam, phenytoin, tolbutamide, and warfarin.

An *in vitro* study showed that the N-acetyl metabolite of ezogabine (NAMR) may inhibit renal clearance of digoxin. Administration of ezogabine at therapeutic doses may increase digoxin serum concentrations. Serum levels of digoxin should be monitored.[154]

There is concern related to increased risk of failure of oral contraceptives with use of cytochrome P450 3A4 enzyme-inducing AEDs, such as phenobarbital, carbamazepine, phenytoin, felbamate (Felbatol), topiramate (Qudexy XR, Topamax, Trokendi XR), oxcarbazepine (Trileptal, Oxtellar XR), eslicarbazepine acetate (Aptiom), clobazam (Onfi), perampanel (Fycompa), and rufinamide (Banzel).[155, 156] Since a particular antiepileptic drug may induce metabolism of the estrogen or the progestin and it is unclear which component is clinically more important in pregnancy prevention, it is recommended that women taking enzyme-inducing antiepileptic drugs should receive an oral contraceptive containing at least 50 mcg of ethinyl estradiol and that low-dose formulations should generally be avoided. Patients taking an oral contraceptive and rufinamide are recommended to use a secondary non-hormonal form of contraception. Antiepileptic drugs that do not induce cytochrome P450 3A4 enzymes, including valproic acid, gabapentin (Neurontin), levetiracetam (Keppra, Keppra XR), tiagabine, zonisamide, vigabatrin, ezogabine (Potiga), and pregabalin (Lyrica), do not interact with oral contraceptives. Lamotrigine (Lamictal, Lamictal XR) levels are reduced by 50 percent with use of oral contraceptives. Therefore, dose adjustment of lamotrigine may be required when oral contraceptives are initiated or discontinued, and it should be noted that clinical toxicity could occur during the placebo or pill-free week of the oral contraceptive regimen.[157]

Medications metabolized through CYP2D6 may need to be adjusted when administered with clobazam (Onfi). Additionally dosage adjustments of clobazam should occur when administered with strong inhibitors of CYP2C19 (e.g. fluconazole, fluvoxamine, ticlopidine), or moderate inhibitors (e.g. omeprazole). Administration with alcohol increases the maximum plasma exposure of clobazam by 50 percent.

Phenytoin is metabolized by CYP2C9 and CYP2C19, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibitory interactions may produce significant increases in circulating phenytoin concentrations and drug toxicity. Phenytoin is also a potent inducer of hepatic drug-metabolizing enzymes and administration may affect exposures to other drugs. Phenytoin also is extensively bound to serum plasma proteins and is subject to displacement.[158]

Drugs that may increase phenytoin serum levels, include: acute alcohol intake, various anti-epileptic agents, azoles and a number of other agents. Drugs that may decrease phenytoin levels, include: anticancer drugs, carbamazepine, chronic alcohol abuse, vigabatrin and other agents. Preparations that increase gastric pH may affect phenytoin absorption, and usually results in a decrease in phenytoin bioavailability.

Phenobarbital, sodium valproate, and valproic acid may either increase or decrease phenytoin concentrations. Similarly, the effect of phenytoin on these agents is unpredictable.

The efficacy of azoles, corticosteroids, estrogens and oral contraceptives as well as a number of other drugs including paclitaxel, paroxetine, quinidine, rifampin, sertraline, teniposide, and theophylline may be impaired by phenytoin.

Increased and decreased PT/INR responses have also been reported when coadministered with warfarin. In addition administration of enteral feedings and nutritional supplements may decrease phenytoin levels.

Due to the high incidence of seizures, neurologic disorders such as peripheral neuropathies, and psychiatric conditions, it is estimated that as many as 55 percent of HIV/AIDS patients may receive both anticonvulsant medications and antiviral therapy.[159] Thus, anticonvulsants that induce P450s such as phenobarbital, carbamazepine, and phenytoin may be expected to decrease exposures to nonnucleotide reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), which could result in therapeutic failure. Alternatively, in some cases, anticonvulsants may reduce the clearance of antiviral agents and induce toxicities. Consequently, it may be important to avoid enzyme-inducing anticonvulsants in people on antiretroviral regimens that include PIs or NNRTIs. If such regimens are required for seizure control, pharmacokinetic monitoring may be necessary to ensure efficacy of the antiretroviral regimen.

Drug Interactions Table

Drug	Substrate	Inhibitor	Inducer
barbiturates[160]	--	--	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5-7
hydantoins[161, 162, 163]	CYP 2C9, 2C19	--	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5-7
succinimides[164]	CYP 3A4	--	CYP 3A4 (methsuximide only)
benzodiazepines[165, 166]	CYP 3A4 (clonazepam, clobazam) CYP 2B6, 2C19 (clobazam, diazepam) CYP 2C8, 2C9, 3A4, 3A5-7 (diazepam),	CYP 2C19, 3A4 (diazepam) CYP2D6 (clobazam)	CYP 3A4 (clobazam)
Carbamazepine Derivatives			
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro, Epitol)[167, 168, 169, 170]	CYP 3A4	--	CYP 1A2, 3A4
eslicarbazepine acetate (Aptiom)[171]	--	CYP 2C19	CYP 3A4, UDPGT 1A1
oxcarbazepine (Trileptal, Oxtellar XR)[172, 173]	--	CYP 2C19	CYP 3A4/5
Valproic Acid Derivatives			
valproic acid, divalproex sodium, valproic acid ER (Depakene, Depakote, Depakote ER, Stavzor)[174, 175, 176, 177]	CYP 2C19	CYP 2C9, 2D6, 3A4	--
Other Anticonvulsants			
ezogabine (Potiga)[178]	Primarily N-acetyltransferase 2 (NAT2) and UGT1A4	--	--
felbamate (Felbatol)[179]	--	CYP 2C19	--
gabapentin (Neurontin)[180]	Not metabolized		
lacosamide (Vimpat)[181]	CYP 2C9, 2C19, 3A4	--	--
lamotrigine (Lamictal, Lamictal XR)[182, 183]	Greater than 75 percent metabolized in the liver by glucuronic acid conjugation; autoinduction may occur		
levetiracetam (Keppra, Keppra XR)[184]	Not extensively metabolized and not dependant on the CYP 450 isoenzymes		
perampanel (Fycompa)[185]	CYP 3A4/5	--	CYP 3A4/5 UDPGT 1A1
pregabalin (Lyrica)[186]	Not metabolized		
rufinamide (Banzel)[187]	--	CYP 2E1	CYP 3A4
tiagabine (Gabitril)[188]	CYP 3A4 possibly: 1A2, 2D6, 2C19	--	--
topiramate (Qudexy XR, Topamax, Trokendi XR)[189, 190]	CYP 2C19	CYP 2C19	CYP 3A4
vigabatrin (Sabril)[191]	Not extensively metabolized, but may induce CYP 2C enzymes in some patients		

zonisamide (Zonegran)[192]	CYP 3A4	--	--

ADVERSE EFFECTS

Drug	Nausea	Diarrhea	Weight Change	Tremor	Somnolence	Dizziness
Benzodiazepine Derivatives						
clobazam (Onfi)[193]	nr	nr	nr	nr	22	reported
clonazepam [194] (Klonopin)	reported	reported	reported	reported	7	<1
diazepam rectal gel (Diastat)[195]	nr	4	nr	nr	23	3
Carbamazepine Derivatives						
carbamazepine (Tegretol/XR, Carbatrol)[196,197]	reported	reported	nr	nr	reported	reported
carbamazepine (Equetro)[198]	29	10	nr	nr	32	44
eslicarbazepine acetate (Aptiom)[199]	10-16 (5)	2-4 (3)	nr	2-4 (1)	11-18 (8)	20-28 (9)
oxcarbazepine (Oxtellar XR)[200,]	12	nr	nr	5 (1,200 mg/d) 1 (2,400 mg/d)	12 (1,200 mg/d) 14 (2,400 mg/d)	20 (1,200 mg/d) 41 (2,400 mg/d)
oxcarbazepine (Trileptal)[201]	16	7	+ 2	4	28	22
Valproic Acid Derivatives						
valproic acid (Depakene)[202] divalproex sodium (Depakote/ER)[203,204] valproic acid ER (Stavzor)[205]	34	23	+ 9	57	30	18
Other Anticonvulsants						
ezogabine (Potiga)[206]	6-9	nr	weight gain 2-3	3-12	15-27	15-32
felbamate (Felbatol)[207]	reported	5.2	weight loss 3.4	reported	reported	reported
gabapentin (Neurontin)[208]	reported	reported	+ 2.9	6.8	19.3	17.1
lacosamide (Vimpat)[209]	7-17 (4)	3-5 (3)	nr	4-12 (4)	5-8 (5)	16-53 (8)
lamotrigine (Lamictal) [210]	7	5	- 5	nr	nr	7
lamotrigine (Lamictal XR) [211]	7 (8)	2 (5)	+ 2 (+ 1)	7 (2)	7 (2)	19 (5)
levetiracetam (Keppra)[212]	5	8	+ >1	>1	15	9
levetiracetam XR (Keppra XR)[213]	5 (3)	nr	nr	nr	8 (3)	5 (3)
perampanel (Fycompa)[214]	3-8 (5)	nr	+ 4 (1)	nr	9-18 (7)	16-43 (0)
pregabalin (Lyrica)[215]	nr	nr	+ 4	8	7-20	10-39
rufinamide (Banzel)[216]	7-12	nr	nr	6	11-17	8-19

Adverse Effects (continued)

Drug	Nausea	Diarrhea	Weight Change	Tremor	Somnolence	Dizziness
Other Anticonvulsants *(continued)*						
tiagabine (Gabitril)[217]	11	2-10	nr	9-21	18-21	27-31
topiramate (Qudexy XR, Topamax, Trokendi XR)[218,219,220]	10-12	5-6	weight loss 9-13	9	9-15	13-14
vigabatrin (Sabril)[221]	2-10 (8)	10-16 (7)	+6 - +14 (+3)	15-16 (8)	22-26 (13)	24-26 (17)
zonisamide (Zonegran)[222]	9	5	weight loss 3	nr	17	13

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

The adverse events for barbiturates, hydantoins, succinimides, and benzodiazepines are not quantified in the majority of the package inserts, but rather listed as occurring or not in a review of systems.

Carbamazepine (Tegretol, Tegretol XR, Carbatrol, and Equetro) may induce hyponatremia similar to the Syndrome of Inappropriate Antidiuretic Hormone release (SIADH). Rashes are frequent, occurring in up to 9.9 percent of patients. Hematological adverse effects have also been reported. Agranulocytosis and aplastic anemia are rare. Thrombocytopenia and anemia have an incidence of less than five percent and usually respond to a cessation of therapy. Leukopenia is the most common hematological side effect with a ten percent incidence. It is usually transient, persisting in about two percent of patients.[223]

Similar to carbamazepine, oxcarbazepine (Trileptal, Oxtellar XR) and eslicarbazepine acetate (Aptiom) are associated with hyponatremia (25 percent and 1.5 percent respectively); this incidence does increase with age. Thirty percent of patients that have experienced a skin rash with carbamazepine will react similarly to oxcarbazepine.[224,225,226]

Common adverse reactions reported in clinical trials with clobazam that occurred at least 10 percent more frequently than placebo, include constipation, somnolence or sedation, pyrexia, lethargy, and drooling.

Felbamate (Felbatol) is associated with a marked increase in the incidence of aplastic anemia (one in 3,000 patients) and hepatitis (one in 10,000 patients).[227] Accordingly, use only in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable in light of the benefits conferred by its use.

Gabapentin (Neurontin) has an 8.3 percent incidence of nystagmus.[228]

Diplopia may occur in six to 16 percent of patients taking lacosamide (Vimpat). Dose-dependent prolongations in PR interval may occur with lacosamide (Vimpat). First-degree AV block was observed in 0.4 percent of patients randomized to lacosamide and zero percent with placebo. Second degree and complete AV block has also been reported, and when given with other drugs that prolong the PR interval, further PR prolongation is possible. Lacosamide may also predispose to atrial arrhythmias

(atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease.[229]

Lamotrigine (Lamictal, Lamictal XR) therapy is associated with rashes; serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine.[230,231] Pediatric patients on adjunctive therapy appear to have a higher risk of serious rash (eight in 1,000 patients) versus adult patients on adjunctive therapy (three in 1,000 patients). Rashes are usually mild to moderate and associated with high initial doses, rapid titration, and concomitant valproate use (including valproic acid and divalproex sodium). SJS and TEN have also occurred with rare deaths reported. Although benign rashes also occur with lamotrigine, it is not possible to reliably predict which rashes will prove to be serious or life-threatening. Accordingly, lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related.

Levetiracetam (Keppra) is associated with a slight decrease in red and white blood cells, but levetiracetam XR (Keppra XR) has not demonstrated this in clinical studies; however, the manufacturer recommends monitoring the cell counts due to the results from the immediate release form. Post-marketing reports have cited hyponatremia as an adverse reaction in patients taking levetiracetam (Keppra) and levetiracetam XR (Keppra XR).[232,233] Post-marketing reports have also shown that levetiracetam (Keppra) is associated with muscle weakness and panic attack in patients.

Post-marketing reports have shown that tiagabine (Gabitril) is associated with seizures and status epilepticus in patients without epilepsy based on experience from off-label use.[234] In most cases, patients were also taking medications known to lower the seizure threshold. Seizures and status epilepticus are known to occur with overdose. Also, tiagabine is associated with cognitive/neuropsychiatric adverse events such as impaired concentration, speech or language problems, confusion, somnolence and fatigue. These adverse events have led to six percent of patients receiving tiagabine versus two percent of patient receiving placebo to discontinue treatment during controlled clinical trials.

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin (Lyrica). Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Pregabalin should be discontinued immediately in patients with these symptoms. Exercise caution when prescribing pregabalin to patients with a history of angioedema or who are already taking medications associated with angioedema such as angiotensin-converting enzyme (ACE) inhibitors.

Topiramate (Qudexy XR, Topamax, Trokendi XR) is a carbonic anhydrase inhibitor. There is an increased rate of kidney stone formation (reduced urinary citrate excretion and increased urinary pH) with nephrolithiasis occurring in 1.5 percent of patients.[235] Metabolic acidosis (due to renal loss of bicarbonate) may also develop because of carbonic anhydrase inhibition. Oligohidrosis, hyperthermia, and heat stroke have been reported, usually following exposure to elevated environmental temperatures. Finally, there are patients who have developed acute myopia and secondary angle-closure glaucoma. These symptoms seem to occur within the first month of therapy.

Zonisamide (Zonegran) is also a carbonic anhydrase inhibitor and a sulfonamide derivative.[236] It is contraindicated in patients with sulfonamide allergy. Zonisamide causes hyperchloremic, non-anion gap, metabolic acidosis caused by renal bicarbonate loss resulting from its effect on carbonic

anhydrase. Kidney stones are reported in approximately four percent of epilepsy patients on zonisamide.

Thrombocytopenia is common in patients on valproic acid (Depakene, Stavzor) and divalproex (Depakote, Depakote ER).[237,238,239,240] It occurs in about 27 percent of patients and responds to a decrease in dose. Bone marrow changes also occur, as do leukopenia, transient neutropenia, and erythroblastopenia. There are at least ten known metabolites; one may account for the reported fatal hepatotoxicities and is increased during dosing with enzyme-inducing drugs. This risk is higher in children and decreases in older age groups. Life-threatening pancreatitis has also been reported. Hyperammonemia may also occur, especially in patients with underlying urea cycle disorders.

Ezogabine (Potiga) has been associated with urinary retention. In an open-label and placebo-controlled clinical trial, two percent of the patients treated with ezogabine experience urinary retention. Of those two percent, 17 percent required catheterization, with post-void residuals of up to 1,500 mL. Close monitoring is recommended for patients who have other risk factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), patients who are unable to communicate clinical symptoms (e.g., cognitively impaired patients), or patients who use concomitant medications that may affect voiding (e.g., anticholinergics).[241]

The most frequently reported adverse effects of ezogabine have been dizziness (23 percent), somnolence (22 percent) and fatigue (15 percent). Confusion, vertigo, tremor, abnormal coordination, disturbance in attention, gait disturbance, memory impairment, diplopia, blurred vision, asthenia, aphasia, dysarthria and balance disorder have also occurred (four to nine percent).[242]

A drug reaction with eosinophilia and systemic symptoms was seen with ethosuximide (Zarontin).[243]

SPECIAL POPULATIONS[244]

Pediatrics

Barbiturates are used for treatment of epilepsy in children. Dosage recommendations for primidone (Mysoline) exist for neonates, infants, and older children. There are dosage recommendations for phenobarbital for adolescents and older; dosage for infants and children should be individualized.

Dosage of the hydantoins in pediatric patients should be individualized and usually requires serum blood level determinations. Dosage of ethotoin (Peganone) in pediatric patients depends on the age and weight of the patient. Pediatric dosage of phenytoin (Dilantin, Phenytek) is based on weight; children over six years of age and adolescents may require the minimum adult dosage.

Ethosuximide (Zarontin) may be used in children three years of age and older. The initial dose for patients three to six years is 250 mg per day and for patients six years of age and older is 500 mg per day; thereafter, the dose should be individualized based on patient response and plasma level determinations. A smaller capsule providing a lower drug dosage of methsuximide (Celontin) is available for small children; optimal dosage must be determined by trial and should be kept at the lowest dose to control seizures so as to minimize adverse effects.

Specific dosage recommendations for clonazepam (Klonopin) exist for children ten years of age and younger or less than 30 kg body weight. Recommended doses are meant to minimize drowsiness and provide seizure control. Clinical studies have not been conducted to establish the efficacy and safety of diazepam rectal gel (Diastat) or clobazam (Onfi) in children less than two years of age.

Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol) can be used in pediatric patients with specific dosage recommendations for children younger than six years of age, children six to twelve years of age, and children older than twelve years of age. Dosage is ultimately determined by monitoring of blood levels and optimal clinical response. The therapeutic range is the same for both children and adults (4-12 mcg/mL). Carbamazepine ER (Equetro) has not been proven to be safe or effective in children or adolescents.[245]

The safety and effectiveness of eslicarbazepine acetate (Aptiom) has not been established in patients below 18 years of age.

Felbamate (Felbatol) is indicated in children only as adjunctive therapy for treatment of Lennox-Gastaut syndrome in patients two to 14 years of age and older.

Gabapentin (Neurontin) is indicated for treatment of partial seizures in children 12 years of age and older with epilepsy and as adjunctive therapy for treatment of partial seizures in children three to 12 years of age with epilepsy.

Lacosamide (Vimpat) has not been studied in patients 17 years of age and younger.

Lamotrigine (Lamictal) is indicated for treatment of children two years of age and older for approved indications (partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic [PGTC] seizures). Safety and effectiveness in patients less than 18 years of age with bipolar disorder have not been established.

Lamotrigine (Lamictal XR) is not approved for patients younger than 13 years of age.

Levetiracetam (Keppra) is indicated as adjunctive therapy for treatment of myoclonic seizures in adolescents 12 years of age and older with juvenile myoclonic epilepsy.[246] Levetiracetam is also used in the management of partial onset seizures in children one month of age and older with epilepsy and of primary generalized tonic-clonic seizures in children six years of age and older with idiopathic generalized epilepsy. Levetiracetam XR (Keppra XR) is indicated as adjunctive therapy in the treatment of partial seizures in patients 12 years of age and older with epilepsy.[247]

Oxcarbazepine (Trileptal) is indicated as monotherapy for treatment of partial seizures in children four years of age and older and as adjunctive therapy in children two years of age and older with epilepsy.[248] Oxcarbazepine extended-release (Oxtellar XR) is indicated as adjunctive therapy of partial seizures in children ages six to 17 years.[249] In children four to 12 years, weight-adjusted clearance is approximately 40 percent higher than adults. Oxcarbazepine ER has not been studied in children younger than four years of age, and is not approved for children under six, due to the size of the tablet.

Perampanel (Fycompa) is indicated as adjunctive therapy for treatment of partial seizures in children at least 12 years of age with epilepsy. Use in patients less than 12 years of age has not been established.[250]

The pharmacokinetics of pregabalin (Lyrica) have not been adequately studied in children. Tiagabine (Gabitril) is indicated as adjunctive therapy for treatment of partial seizures in children at least 12 years of age with epilepsy.

Rufinamide (Banzel) is indicated for adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in patient four years of age and older.[251] Studies indicate that the pharmacokinetics of rufinamide in pediatric patients and adolescents are similar to adults, but drug interactions tend to be more pronounced in pediatric patients.

Immediate-release topiramate (Topamax) is indicated as initial monotherapy for treatment of partial onset and primary generalized tonic-clonic seizures in children two years of age and older; however, the extended-release formulations (Qudexy XR, Trokendi XR) are only labeled for patients with this indication age 10 years or older. Immediate-release topiramate is also indicated as adjunctive therapy for treatment of partial onset and primary generalized tonic-clonic seizures in children two to 16 years of age and as adjunctive therapy in patients two years of age and older with seizures associated with Lennox-Gastaut syndrome. Trokendi XR is indicated as adjuvant therapy for the treatment of partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in patients six years of age and older; whereas Qudexy XR is indicated for these indications in patients as young as two years of age. Pediatric patients have a 50 percent higher clearance of topiramate which results in a shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. Topiramate is approved for migraine prophylaxis in children 12 years of age and older. In studies, the incidence of cognitive adverse reactions, such as difficulty with concentration and attention, was increased in pediatric patients treated with topiramate, as compared to placebo. Pediatric patients between the ages of 12 and 17 taking topiramate more frequently had elevated BUN, creatinine, uric acid, chloride, ammonia, total protein and platelet levels.[252]

Valproate has not been established to be safe and effective for the treatment of partial seizures in children under the age of 10 years. Safety and efficacy of valproic acid for epilepsy and migraine prophylaxis has not been established in children less than 10 and 16 years of age.

Vigabatrin (Sabril) is approved for use in infants as young as one month to two years for treatment of infantile spasms, and for the adjunctive treatment of refractory complex partial seizures in children ten years of age and older who have inadequately responded to several alternative treatments, if the benefits outweigh the risk of vision loss.[253]

Although off-label use has been reported, safe and effective use of zonisamide (Zonegran) in children less than 16 years of age has not been established. All patients, especially children, should be told to limit exposure to high ambient temperatures or other extremes that might aggravate temperature regulation. Concurrent use of medications that might predispose a patient to heat intolerance (anticholinergics) should be used cautiously with zonisamide (Zonegran).

The safety and effectiveness of ezogabine (Potiga) in patients under 18 years of age have not been established.

Pregnancy

Freedom from seizures is the ultimate goal of treatment of patients with epilepsy; however, adverse effects of the antiepileptic drugs should not outweigh the benefits, particularly in women with epilepsy who wish to become pregnant. These women and their partners need to understand the risks associated with uncontrolled seizures as well as the teratogenicity of some of the antiepileptic drugs.[254]

Barbiturates and hydantoins are all classified as Pregnancy Category D.

Clonazepam, diazepam, carbamazepine, valproic acid, valproic acid ER, divalproex, topiramate and topiramate XR are also classified as Pregnancy Category D. Some studies have indicated a higher risk of birth defects and possibly adverse cognitive effects with exposure to valproate compared to carbamazepine. Further studies are needed; however, it appears to be reasonable to use valproate

with caution in epileptic women who desire to become pregnant with consideration given to possible alternative antiepileptic drugs that may be equally effective and safer. With appropriate counseling, women who need valproate for seizure control should continue the drug and not be discouraged from pregnancy.[255] Due to the risk of birth defects, valproates are classified as Pregnancy Category X for migraine prophylaxis.[256]

All of the drugs in this review of anticonvulsants, other than those named above, are classified as Pregnancy Category C. Although classified as Pregnancy Category C, gabapentin has not been evaluated for use during pregnancy.

A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*.[257] This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Although, oxcarbazepine products are classified as Pregnancy Category C, it should be noted that there are no well-controlled clinical studies of oxcarbazepine in pregnant women; however, oxcarbazepine is structurally closely related to carbamazepine, which is considered to be teratogenic in humans. Given this fact and the results of animal studies, it is likely that oxcarbazepine is a human teratogen. It should be used during pregnancy only if the potential benefit justifies the potential risk.

Physiological changes associated in pregnancy, particularly the third trimester, may decrease plasma levels of levetiracetam. Close monitoring should continue during pregnancy and the postpartum period.[258]

Renal Impairment

Dosage of phenobarbital should be reduced in patients with impaired renal function.

Ethosuximide and methsuximide should be administered with extreme caution to patients with known renal disease. Periodic urinalysis tests should be performed for patients on these drugs. Ethosuximide and methsuximide do not have guidelines available for dose adjustment in patients with renal dysfunction.

Metabolites of clonazepam and diazepam are excreted by the kidneys; therefore, caution should be exercised in treating patients with impaired renal function. Clobazam does not require dosage adjustment in those with mild to moderate renal impairment, but this medication has not been studied in severe impairment of end-stage renal disease (ESRD).

Felbamate should be used with caution in patients with renal dysfunction.

Dosage adjustments are recommended for gabapentin in patients with compromised renal function. Gabapentin has not been studied in pediatric patients with renal insufficiency.

The maximum dose of lacosamide (Vimpat) in patients with severe renal impairment is 300 mg/day. Lacosamide is removed by hemodialysis and a bolus of 50 percent of the dose is recommended after each dialysis session. Patients with severe renal impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 may have a significant increase in exposure to lacosamide and dose reduction may be necessary.

Lamotrigine has not been extensively evaluated in patients with severe renal function impairment; therefore, this medication should be used cautiously in these patients.

Dosing of levetiracetam must be individualized based on a patient's renal function.

In patients with impaired renal function (creatinine clearance less than 30 mL/min), oxcarbazepine and oxcarbazepine ER (Oxtellar XR) therapy should be initiated at 50 percent of the usual starting dose and titrated slowly to achieve the desired clinical response. In dialysis patients with end-stage renal disease, immediate-release oxcarbazepine (Trileptal) is recommended instead of oxcarbazepine ER.[259]

Eslicarbazepine (Aptiom) clearance is decreased in patients with impaired renal function. Dosage adjustment is necessary in patients with CrCL <50 mL/min. In ESRD, repeated hemodialysis removed eslicarbazepine metabolites from the systemic circulation.[260] Maximum dose of eslicarbazepine in patients with moderate to severe renal impairment is 600 mg once daily.

Dose adjustment of perampanel (Fycompa) is not required in mild renal impairment.[261] In patients with moderate renal impairment, close monitoring and slower titration should be considered. Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended.

Adverse reactions to pregabalin are dose-dependent, and it is eliminated primarily by renal excretion; therefore, dosage should be adjusted based on renal function as determined by creatinine clearance.

No dosage adjustment is necessary in patients taking rufinamide with impaired renal function (creatinine clearance less than 30 mL/min), but hemodialysis has reduced the rufinamide exposure by about 30 percent. Adjustment of the dose during dialysis may be considered.

In patients with impaired renal function, 50 percent of the topiramate dose is recommended. Renally impaired patients will require a longer time to reach steady state at each dose.

Information about how to adjust the vigabatrin dose in pediatric patients with renal impairment is unavailable. In adults, dose adjustment is necessary in patients with mild, moderate, and severe renal impairment.

Since zonisamide is excreted by the kidneys, patients with renal disease should be treated with caution; titration may need to be slower and monitoring more frequent.

Ezogabine (Potiga) should be used cautiously in patients with renal impairment. Dosage adjustments are recommended in patients with moderate or severe renal impairment (CrCL < 50 mL/min) including patients with end-stage renal disease (renal failure) receiving dialysis.

Hepatic Impairment

Dosage of phenobarbital should be reduced in patients with impaired hepatic function.

Liver function tests should be performed if clinical evidence of liver dysfunction exists during therapy with ethotoin. Signs of liver damage are justification for discontinuation of therapy.

The liver is the primary site of phenytoin biotransformation; therefore, patients with impaired hepatic function may show early signs of toxicity. As with all patients, phenytoin serum level concentrations should be monitored for optimal clinical effect and safe use of the medication. Phenytoin is highly protein bound and the free fraction changes in the presence of low albumin levels. Consequently, free rather than total phenytoin concentration should be monitored in the presence of low albumin levels.

Ethosuximide and methsuximide should be administered with extreme caution to patients with impaired hepatic function. Periodic liver function tests should be performed for patients on these drugs.

Clonazepam undergoes hepatic metabolism; therefore, it should not be used in treating patients with impaired hepatic function. Similarly, dosing for initial clobazam (Onfi) should be decreased to 5 mg/day for those patients with mild to moderate hepatic insufficiency. Limited information for administration of clobazam is available for those with severe hepatic impairment, so dosing recommendations cannot be made.

Felbamate should not be prescribed for anyone with a history of hepatic dysfunction as it carries a boxed warning related to hepatic failure.

Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine (Trileptal) in hepatically-impaired patients after a single 900 mg oral dose, and no dose adjustment is recommended in patients with mild to moderate impairment.[262] The pharmacokinetics of oxcarbazepine and the active metabolite, MHD, have not been evaluated in patients with severe hepatic impairment. Caution should be exercised when dosing immediate-release oxcarbazepine in severely impaired patients, and oxcarbazepine ER (Oxtellar XR) is not recommended in patients with severe hepatic impairment.[263]

Dose adjustments of eslicarbazepine acetate (Aptiom) are not required in patients with mild to moderate hepatic impairment. Use in patients with severe hepatic impairment has not been studied, and is not recommended.[264]The maximum dose of lacosamide (Vimpat) in patients with mild to moderate hepatic impairment is 300 mg/day. Use is not recommended in severe hepatic impairment. Patients with hepatic impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 may have a significant increase in exposure to lacosamide and dose reduction may be necessary.

Initial, escalation, and maintenance doses of lamotrigine should be reduced by 25 percent in patients with moderate and severe hepatic function impairment without ascites and by 50 percent in patients with severe hepatic function impairment with ascites.

Due to higher exposures and a longer half-life of perampanel (Fycompa), dosage adjustment is recommended in patients with mild and moderate hepatic impairment receiving perampanel.[265] Maximum recommended daily dose is 6 mg and 4 mg once daily for patients with mild and moderate hepatic impairment, respectively. Use in patients with severe hepatic impairment is not recommended.

The effects of hepatic impairment on the pharmacokinetics of rufinamide have not been studied, therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

Patients with impaired hepatic function may require reduced initial and maintenance doses of tiagabine and/or longer dosing intervals.

Liver disease impairs the capacity to eliminate valproate. Liver impairment is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Therefore, monitoring of total concentrations may be misleading because free concentrations may be significantly increased in patients with hepatic disease whereas total concentrations may appear to be normal. Liver function tests should be performed prior to therapy with valproate and at frequent intervals thereafter, especially during the first six months of therapy.

Since zonisamide is metabolized by the liver, patients with hepatic disease should be treated with caution. Titration may need to be slower and monitoring more frequent.

In patients with moderate or severe hepatic impairment, the initial maintenance dose of ezogabine (Potiga) should be adjusted. Patients with moderate (Child-Pugh >7-9) or severe (Child-Pugh >9) hepatic impairment should initiate therapy at 50 mg three times daily and then be titrated according to the standard ezogabine titration schedule to a maximum dose of 250 mg or 200 mg three times daily, respectively.

The clearance of topiramate may be decreased in patients with hepatic impairment; however the mechanism is not well understood and no dose adjustments are required.

DOSAGES

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Barbiturates*				
primidone (Mysoline)[266]	100-125 mg	2,000 mg/day (three times daily)	Under 8 years of age: 10-25 mg/kg/day	50, 250 mg tablets
phenobarbital[267]	10-20 mg/kg (load), then 1-3 mg/kg/day	180-300 mg/day (one to two times daily)	3-8 mg/kg/day	20 mg/5 mL elixir 15, 16.2, 30, 32.4, 60, 65, 97.2 100 mg tablets
Hydantoins				
ethotoin (Peganone)[268]	250 mg four times a day	3 grams daily in four to six divided doses	500-1,000 mg daily	250 mg tablets
phenytoin (Dilantin)[269, 270, 271]	100 mg three times a day	600 mg/day (three to four times daily; convert to once daily with Kapseal)	4-8 mg/kg/day	30, 100 mg phenytoin sodium ER Kapseals* 50 mg phenytoin base chewable tablets* 125 mg/5 mL phenytoin base suspension*
phenytoin (Phenytek)[272]	100 mg three times a day	600 mg/day (three to four times a day and then convert to once daily)	4-8 mg/kg/day	200 mg, 300 mg phenytoin sodium ER capsules*
Succinimides				
ethosuximide (Zarontin)[273, 274]	250-500 mg/day	1.5 gm/day or until control is achieved with minimal side effects (two times a day)	20 mg/kg/day	250 mg capsules 250 mg/5 mL syrup/solution
methsuximide (Celontin)[275]	300 mg daily	1.2 gm/day or until control is achieved with minimal side effects (two to four times a day)	Dosing not specified in label	300 mg capsules
Benzodiazepines				
clobazam (Onfi)[276]	≤ 30 kg: 5 mg/day >30 kg: 10 mg/day Poor CYP2C19 metabolizers: 5mg/day	≤ 30 kg: 20 mg/day >30 kg: 40 mg/day	≤ 30 kg: 20 mg/day >30 kg: 40 mg/day	10, 20 mg tablets 2.5 mg/mL suspension
clonazepam (Klonopin)[277, 278]	0.5 mg three times a day	20 mg/day (three times a day)	0.1-0.2 mg/kg/day	0.5, 1, 2 mg tablets 0.125, 0.25, 0.5, 1, 2 mg orally disintegrating tablets (wafers)
diazepam rectal gel (Diastat)[279]	0.2 mg/kg one time and may repeat in four to 12 hours if needed	One episode every five days or five episodes every month	0.2-0.5 mg/kg	2.5 mg Twin Pack 10, 20 mg Acudial

Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Carbamazepine Derivatives				
carbamazepine (Tegretol/XR, Carbatrol, Epitol)[280,281,282]	**Epilepsy:** 400 mg/day (200 mg twice daily for both IR and ER; give suspension 100 mg four times daily) May increase dose weekly by adding up to 200 mg/day; use a twice daily regimen for ER tablets or three to four times daily for other formulations **Trigeminal neuralgia:** 200 mg/day (100 mg twice daily for both IR and XR; give Carbatrol 200 mg one time on first day; give suspension 50 mg four times daily)	**Epilepsy:** 1,600 mg/day (twice daily for XR/ER and three to four times a day for IR) Trigeminal neuralgia: 1,200 mg/day	**Children < 6 years:** Initially, 10 to 20 mg/kg/day twice daily or three times daily as tablets or four times daily as suspension. May increase dose weekly up to 35 mg/kg/day **Children 6-12 years:** Initially, 100 mg twice daily IR or ER tablets or 2.5 mL four times daily for suspension. May increase dose weekly by adding up to 100 mg/day using twice daily regimen of ER tablets or three to four times daily of other formulations up to 1,000 mg/day	200 mg tablets 100 mg chewable tablets 100 mg/5 mL suspension 100, 200, 400 mg XR tablets 100, 200, 300 mg ER capsules
carbamazepine (Equetro)[283]	**Bipolar Disorder:** 400 mg/day (twice a day)	**Bipolar Disorder:** 1,600 mg/day (twice a day)	--	100, 200, 300 mg ER capsules
eslicarbazepine acetate (Aptiom)[284]	400 mg once daily. After one week, increase to 800 mg once daily	1,200 mg once daily	--	200, 400, 600, 800 mg tablets
oxcarbazepine ER (Oxtellar XR)[285]	600 mg (once daily) on an empty stomach May increase dose weekly by adding up to 600 mg/day (once daily)	2,400 mg/day (once daily) on an empty stomach	≥ 6 years Initially, 8 to 10 mg/kg/day (once daily) on an empty stomach May increase dose weekly by 8 to 10 mg/kg increments (once daily) on an empty stomach, up to 600mg/day. Weight dependent targets range 900-1,800 mg/day (once daily)	150, 300, 600 mg ER tablets

Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Carbamazepine Derivatives *(continued)*				
oxcarbazepine (Trileptal)[286]	300 mg twice a day	2,400 mg/day (twice a day)	Weight dependent targets range 900-2,100 mg/day	150, 300, 600 mg tablets 300 mg/5 mL suspension
Valproic Acid and Derivatives				
valproic acid (Depakene)[287]	10-15 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	60 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	10-15 mg/kg/day	250 mg capsules 250 mg/5 mL syrup
valproic acid ER (Stavzor)[288]	10-15 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	60 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	≥10 years: 10-15 mg/kg/day	125, 250, 500 mg delayed-release capsules
divalproex (Depakote/ER)[289, 290, 291]	10-15 mg/kg/day	60 mg/kg/day (delayed release dosed twice a day; ER dosed once daily)	≥10 years: 10-15 mg/kg/day	125, 250, 500 mg delayed-release tablets 125 mg Sprinkle capsules 250, 500 mg ER tablets
Other Anticonvulsants				
ezogabine (Potiga)[292]	300 mg/day (100 mg three times a day)	1,200 mg/day (400 mg three times a day)	--	50, 200, 300, 400 mg tablets
felbamate (Felbatol)[293]	1,200 mg/day (three to four times a day)	3,600 mg/day (three to four times a day)	15 to 45 mg/kg/day	400, 600 mg tablets 600 mg/5 mL suspension
gabapentin (Neurontin)[294]	300 mg three times a day	3,600 mg/day (three times a day)	up to 50 mg/kg/day	100, 300, 400 mg capsules 600, 800 mg tablets 250 mg/5 mL solution
lacosamide (Vimpat)[295]	50 mg twice daily	200-400 mg daily in two divided doses	--	50, 100, 150, 200 mg tablets 10 mg/mL solution

Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Other Anticonvulsants *(continued)*				
lamotrigine (Lamictal)[296]	Not in combination with enzyme inducing drugs or valproate 25 mg/day With valproate 25 mg every other day With enzyme inducers and not valproate 50 mg/day	**Bipolar Disorder:** Not in combination with enzyme inducing drugs or valproate 200 mg/day With valproate 100 mg/day With enzyme inducers and not valproate 400 mg/day **Epilepsy:** With valproate alone: 200mg/day With enzyme inducers: 500 mg/day	**For Children 2-12 years not taking valproate or glucuronidase inducers:** 4.5 to 7.5 mg/kg/day (max 300 mg/day in 2 divided doses) **With glucuronidase inhibitors (e.g. valproate) and no inducers** 1 to 5 mg/kg/day (max 200 mg/day in 1 or 2 divided doses) **With glucuronidase inducers (carbamazepine, phenytoin, phenobarbital, or primidone) and no inhibitors** 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses)	25, 100, 150, 200 mg tablets 5, 25 mg chewable tablets 25, 50, 100, 200 mg ODT
lamotrigine (Lamictal XR)[297]	one tablet daily (Daily dosage same as Lamictal immediate release tablets)	one tablet daily (Daily dosage same as Lamictal immediate release tablets)	one tablet daily (Daily dosage same as Lamictal immediate release tablets)	25, 50, 100, 200, 250, 300 mg tablets

Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	How Supplied
Other Anticonvulsants *(continued)*				
levetiracetam (Keppra)[298]	500 mg twice a day	1,500 mg twice a day	**Adjunctive therapy for partial seizures:** 1 month to <6 months: initial -7mg/kg twice daily; recommended – 21 mg/kg twice daily 6 months to <4 years: initial - 10 mg/kg twice daily; recommended – 25 mg/kg twice daily 4 to <16 years: initial - 10 mg/kg twice daily; recommended – 30 mg/kg twice daily **Adjunctive therapy for myoclonic seizures:** 12 years and older: initial – 500 mg twice daily; recommended – 1500 mg twice daily	250, 500, 750, 1,000 mg tablets 100 mg/mL solution
levetiracetam XR (Keppra XR)[299]	1,000 mg once daily	3,000 mg once daily	12 years and older same as in adults	500, 750 mg tablets
perampanel (Fycompa)[300]	2 mg once daily at bedtime, and 4 mg in patients on enzyme inducing AEDs	12 mg once daily at bedtime	12 years and older same as in adults	2, 4, 6, 8, 10, 12 mg tablets
pregabalin (Lyrica)[301]	**Adjunctive therapy for partial seizures:** 150 mg/day in two to three divided doses	**Adjunctive therapy for partial seizures:** 600 mg/day	--	25, 50, 75, 100, 150, 200, 225, 300 mg capsules 20 mg/mL solution
rufinamide (Banzel)[302]	400-800 mg/day in two equally divided doses with food.	3,200 mg/day in two equally divided doses with food.	≥4 years: 10 mg/kg/day in two equally divided doses. Maximum 45 mg/kg/day or 3,200 mg in two equally divided doses with food.	200, 400 mg tablets 40 mg/mL suspension

Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	How Supplied
Other Anticonvulsants *(continued)*				
tiagabine (Gabitril)[303]	4 mg/day (with enzyme-inducing antiepileptic drugs	56 mg/day (with enzyme-inducing antiepileptic drugs) (two to four times a day)	12-18 years up to 32 mg/day (with enzyme-inducing antiepileptic drugs)	2, 4, 12, 16 mg tablets
topiramate (Topamax)[304]	25-50 mg/day in two divided doses	400 mg/day in two divided doses	5-9 mg/kg/day in two divided doses 2-10 years of age 25mg/day nightly for the first week and titrated based on tolerance and seizure control maximum dose based on weight **Migraine Prophylaxis:** 12 years and older 100 mg in two divided doses	25, 50, 100, 200 mg tablets 15, 25 mg sprinkle capsules
topiramate XR (Qudexy XR)[305]	25-50 mg daily	400 mg daily	5-9 mg/kg once daily 2 years of age and older 25 mg/day nightly for the first week and titrated based on tolerance and seizure control maximum dose based on weight	25, 50, 100, 150, 200 mg capsules
topiramate XR (Trokendi XR)[306]	25-50 mg daily	400 mg daily	5-9 mg/kg once daily 6 years of age and older 25mg/day nightly for the first week and titrated based on tolerance and seizure control maximum dose based on weight	25, 50, 100, 200 mg capsules

Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	How Supplied
Other Anticonvulsants *(continued)*				
vigabatrin (Sabril)[307]	500 mg twice daily	1.5 g twice daily	**10-16 years of age and 25–60 kg:** 250 mg twice daily) titrated to a maximum 1 g twice daily **Infantile Spasms:** 50 mg/kg/day in two divided doses, titrated to a maximum of 150 mg/kg/day	500 mg tablets 500 mg powder for oral solution
zonisamide (Zonegran)[308]	100 mg daily	600 mg/day (one to two times a day)	--	25, 50, 100 mg capsules

* Dilantin is available as 30 mg and 100 mg Extended-Release Kapseals expressed in terms of phenytoin sodium. Whereas the 50 mg chewable tablets and 125 mg/ 5 mL suspension are immediate-release formulations expressed in terms of phenytoin base. Interchange of the immediate-release and extended release formulations require not only accounting for differences in the frequency of administration but also that the ER formulations are 92% of the labeled dose in terms of phenytoin base as compared to 100% of the labeled dose as phenytoin base for the immediate-release formulations. Failure to adjust for this difference when switching formulations can result in toxicity or loss of efficacy due to the narrow therapeutic range and the nonlinear kinetics often observed with clinical dosages. Phenytek is also only available as extended-release capsules of phenytoin sodium expressed in terms of the salt. Dosage changes may need to be made for each agent based on the other anticonvulsants that the patient is currently receiving, decreased renal and/or hepatic function, and tolerability of the agent. Please consult package inserts for additional information.

carbamazepine: When converting patients from carbamazepine IR to Tegretol XR or Carbatrol, the same total daily dose should be administered. Tegretol XR tablets must be swallowed whole and never crushed or chewed.

ezogabine: In clinical trials, ezogabine 400 mg three times daily, when compared to 300 mg three times daily, did not result in additional improvement in seizure reduction, but was associated with an increase in adverse events and discontinuations.

oxcarbazepine ER: In conversion of oxcarbazepine immediate-release to extended-release (Oxtellar XR), higher doses of Oxtellar XR may be needed, as the ER product is not bioequivalent to the same total dose of IR formulation.

phenytoin: Dilantin Kapseals and Phenytek are extended-release capsules formulated with the sodium salt of phenytoin. They are initiated three times daily, and then the patient is converted to once daily dosing when adequate seizure control is attained. The free acid form of phenytoin is used in the Dilantin-125 Suspension and Dilantin Infatab formulations. There is an eight percent increase in drug with the free acid products. They are not to be used for once daily dosing.

valproic acid and derivatives: There are several derivatives of valproic acid available. Each equivalent dosage form (Depakene versus Depakote) delivers the same amount of valproate ion. Depakote causes fewer gastrointestinal adverse effects than Depakene.

When converting patients from twice daily Depakote to once daily Depakote ER, an 8 to 20 percent higher total daily dose of Depakote ER should be given. They are not bioequivalent and dosage adjustments may be required.

In addition to its use in epilepsy, divalproex ER (Depakote ER) is indicated for use in acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. The initial dose is 25 mg/kg/day and can be increased to a maximum of 60 mg/kg/day to achieve therapeutic response. It is also indicated for migraine prophylaxis; the starting dose is 500 mg daily for one week, and then 1,000 mg daily.

vigabatrin: Vigabatrin is only available through a special restricted distribution program called SHARE program.

CLINICAL TRIALS

Search Strategy

Due to the multiple indications for use of the anticonvulsant medications, many of the comparative clinical trials currently available do not specifically focus on treatment of seizure disorder. However, the studies identified in this review attempt to isolate those comparative studies that facilitate identification of the clinically proven therapies in the treatment of seizure disorder that meet the goals of treatment for seizure disorder: reducing the frequency of seizures and providing the optimal quality of life for the patient. When comparative trial information was unavailable, well-designed placebo-controlled studies have been included.

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the use of all drugs in this class and the keywords "seizure" and "anticonvulsants". Randomized, controlled, comparative trials of FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Good quality, double-blind, comparative trials have not been performed with divalproex, carbamazepine, and lamotrigine in the management of bipolar disorder.

ethosuximide (Zarontin), valproic acid (Depakene), and lamotrigine (Lamictal)

In a double-blind, randomized, controlled clinical trial, the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine in children with newly diagnosed childhood absence epilepsy (n=453) were compared.[309] Drug doses were increased until the child was free of seizures, the maximal allowable or highest tolerable dose was reached, or a criterion indicating treatment failure was met. The primary outcome was freedom from treatment failure after 16 weeks of therapy. Differential drug effects were determined by means of pairwise comparisons. After 16 weeks of therapy, the freedom-from-failure rates for ethosuximide and valproic acid were similar (53 and 58 percent, respectively; $p=0.35$) and were higher than the rate for lamotrigine (29 percent; $p<0.001$ for both comparisons). There were no significant differences among the three drugs with regard to discontinuation because of adverse events. Lamotrigine is not indicated for the treatment of absence seizures.

gabapentin (Neurontin) and carbamazepine (Tegretol)

Gabapentin and carbamazepine have been compared in a randomized, double-blind manner for the treatment of partial or generalized epilepsy in 292 patients.[310] They were similar in efficacy with more carbamazepine patients discontinuing therapy due to adverse effects than gabapentin patients (24 percent versus 13.5 percent).

lamotrigine (Lamictal), carbamazepine (Tegretol), and phenytoin (Dilantin)

Lamotrigine has been compared to carbamazepine (n=150) and to phenytoin (n=181) in two separate randomized, double-blind trials for treatment of partial or generalized epilepsy.[311,312] Similar efficacy is noted among the agents with lamotrigine better tolerated. Nineteen percent of carbamazepine patients reported rash versus three percent of lamotrigine patients. In the comparative trial with phenytoin, 14 percent of lamotrigine and nine percent of phenytoin patients reported a rash. In the study, the 100 mg per day starting dose for lamotrigine was higher than currently recommended.

gabapentin (Neurontin), lamotrigine (Lamictal) and carbamazepine (Tegretol)

An 18-center, randomized, double-blind, double-dummy, parallel study of 593 elderly patients with newly diagnosed seizure disorder was conducted to determine the relative tolerability and efficacy of two anticonvulsants, lamotrigine and gabapentin, as compared to carbamazepine.[313] Patients (mean age 72 years) were randomly assigned to one of three treatment groups: gabapentin 1,500 mg daily, lamotrigine 150 mg daily, and carbamazepine 600 mg daily. The primary outcome measure was retention in the trial for at least 12 months. Most patients had multiple medical conditions, received an average of seven concomitant medications, and had a history of cerebral infarction. There was no significant difference in seizure-free rate at 12 months. However, the incidence of adverse effects that resulted in termination of therapy was 12.1 percent for lamotrigine, 21.6 percent for gabapentin, and 31 percent for carbamazepine (p=0.001). The study concluded that lamotrigine and gabapentin should be considered as initial therapy for older patients with newly diagnosed seizures.

lamotrigine (Lamictal) and valproic acid (Depakene)

Lamotrigine has also been compared to valproic acid as monotherapy in refractory partial epilepsy in a randomized, double-blind trial.[314] Lamotrigine 500 mg proved superior to 1,000 mg of valproic acid with 56 percent of the 156 patients completing the study versus 20 percent on valproic acid. Exit criteria were based on worsening seizure activity. Rash was reported by eight percent of valproic acid-treated patients and 11 percent of lamotrigine-treated patients (one with Stevens-Johnson syndrome). The lamotrigine titration rate was higher than currently recommended.

levetiracetam (Keppra) and controlled-release carbamazepine

Adults with two or more partial or generalized tonic-clonic seizures in the previous year were randomly assigned to levetiracetam 500 mg twice daily (n=288) or controlled-release carbamazepine 200 mg twice daily (n=291) in a multicenter, double-blind, noninferiority, parallel-group trial.[315] The dosage could be increased incrementally to a maximum of levetiracetam 1,500 mg twice daily or controlled-release carbamazepine 600 mg twice daily. Patients achieving the primary endpoint of a six-month seizure-free period continued on further treatment for a six-month maintenance period. At per-protocol analysis, 73 percent of levetiracetam patients were seizure-free at six months and 56.6 percent were at one year versus 72.8 percent controlled-release carbamazepine patients were seizure-free at six months and 58.5 percent at one year. Of all patients achieving six-month or one-year remission, 80.1 percent and 86.0 percent in the levetiracetam group and 85.4 percent and 89.3 percent in the carbamazepine group did so at the lowest dose level. Withdrawal rates for adverse events were 14.4 percent with levetiracetam and 19.2 percent with controlled-release carbamazepine.

oxcarbazepine (Trileptal), phenytoin (Dilantin), and valproic acid (Depakene)

Oxcarbazepine has been compared to phenytoin and valproic acid for the treatment of either partial or generalized seizures.[316,317,318] The randomized, double-blind studies show the agents have similar seizure control. More phenytoin patients discontinued therapy due to adverse effects. The early discontinuation rates due to adverse events were similar in the valproic acid study.

Oxcarbazepine has also been compared to carbamazepine for generalized tonic-clonic seizures in newly diagnosed patients in a similar double-blind study (n=235).[319] Sixty percent of patients on carbamazepine and 52 percent of patients on oxcarbazepine remained seizure-free. Twenty-six percent of carbamazepine patients discontinued treatment as compared to 14 percent of oxcarbazepine patients.

topiramate (Topamax) and phenytoin

A randomized, double-blind, 28-day trial of topiramate 100 mg/day versus phenytoin 300 mg/day (after 1,000 mg loading dose) was conducted in 261 patients with new-onset epilepsy.[320] The primary endpoint was time to seizure, and the primary objective was to establish non-inferiority of topiramate to phenytoin in the risk of seizure. At day 28, the estimated seizure-free rate was 81.1 percent for topiramate compared to 90.3 percent for phenytoin. Non-inferiority of topiramate to phenytoin could not be established [hazard ratio 2.0, 95% confidence interval, 0.98 to 4.12, p=0.366; phenytoin was not superior to topiramate. A higher percentage of patients discontinued phenytoin compared to topiramate for all reasons (21.1 versus 12.8 percent) and due to adverse events (13.4 versus 6.8 percent). The most common treatment-related adverse events in both groups were dizziness, paresthesia, and somnolence.

pregabalin (Lyrica) and lamotrigine

A phase 3, double-blind, randomized, multicenter, non-inferiority study compared the efficacy and tolerability of pregabalin and lamotrigine monotherapy in patients with newly diagnosed partial seizures.[321] Patients were titrated to either 75 mg oral pregabalin or 50 mg oral lamotrigine twice daily during a four-week dose-escalation phase, followed by a 52-week efficacy assessment phase where the dose could be increased as needed to a maximum of 600 mg and 500 mg, respectively. The primary efficacy endpoint was the proportion of patients who remained seizure-free for six or more continuous months. Patients (n=660) were randomly assigned to pregabalin or lamotrigine, of whom 622 entered the efficacy assessment phase (314 pregabalin, 308 lamotrigine). Fewer pregabalin patients versus lamotrigine patients became seizure-free for six or more continuous months (162 [52 percent] versus 209 [68 percent]; difference in proportion, -0.16, 95% CI -0.24 to -0.09). The overall incidence of adverse events was similar between groups and consistent with that in previous studies; dizziness (55 [17 percent] versus 45 [14 percent] patients), somnolence (29 [nine percent] versus 14 [four percent]), fatigue (27 [eight percent] versus 19 [six percent]), and weight increase (21 [six percent] versus seven [two percent]) were numerically more common in the pregabalin group than in the lamotrigine group. The authors concluded that pregabalin has similar tolerability but inferior efficacy to lamotrigine for the treatment of newly diagnosed partial seizures in adults.

clobazam (Onfi) and placebo

A randomized double-blind 12-week trial in 238 patients with poorly controlled Lennox-Gastaut Syndrome (LGS) compared adjunctive clobazam to placebo.[322,323] The study included a four-week

baseline period followed by a three-week titration period and 12-week maintenance period. Patients were between the ages of two to 54 years with a current or prior diagnosis of LGS and stratified into two weight groups (12.5 kg to 30 kg versus more than 30 kg). They were then randomized to placebo or one of three target maintenance doses: low, medium or high dose. For the patients of smaller weight, the doses were 5 mg, 10 mg or 20 mg daily. For the patients of higher weight, the doses were 10 mg, 20 mg or 40 mg daily. The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic or myoclonic), also known as drop attacks, from the four-week baseline period to 12-week maintenance period. The pre-dosing baseline average for weekly drop seizure frequency was 98, 100, 61 and 105 for the placebo, low-, medium- and high-dose groups, respectively. There was a decrease of drop seizure frequency of 12.1 percent, 41.2 percent, 49.4 percent and 68.3 percent for the placebo, low-, medium- and high-dose groups, respectively ($p \leq 0.05$). The effects of clobazam appeared to be dose-dependent. There was no evidence that tolerance to the therapeutic effect of clobazam occurred during the three month maintenance period.

Diazepam rectal gel (Diastat) and placebo

In a double-blind, parallel-group, placebo-controlled study of home-based treatment for acute repetitive seizures patients were randomized to receive either rectal diazepam gel (n=64), at a dosage varying from 0.2 to 0.5 mg per kilogram of body weight on the basis of age, or placebo (n=61).[324] Children received one dose at the onset of acute repetitive seizures and a second dose four hours later. Adults received three doses -- one dose at onset, and two more doses 4 and 12 hours after onset. Treatment was administered by a caregiver who had received special training. The number of seizures after the first dose was counted beginning immediately after the first dose and continued for 12 hours in children and 24 hours in adults. Of 125 study patients with a history of acute repetitive seizures (ARS), 91 (47 children and 44 adults) were treated for an exacerbation of seizures during the study period. Diazepam treatment was superior to placebo with regard to the outcome variables related to efficacy: reduced seizure frequency ($p<0.001$) and improved global assessment of treatment outcome by the caregiver (frequency and severity of seizures and drug toxicity) ($p<0.001$). Post hoc analysis showed diazepam to be superior to placebo in reducing seizure frequency in both children ($p<0.001$) and adults ($p=0.02$), but only in children was it superior with regard to improvement in global outcome ($p<0.001$). The time to the first recurrence of seizures after initial treatment was longer for the patients receiving diazepam ($p<0.001$).

eslicarbazepine acetate (Aptiom) and placebo

Eslicarbazepine acetate was compared to placebo as adjunctive therapy in adults with partial-onset seizures in three randomized, double-blind, placebo-controlled trials.[325] Enrolled subjects had partial-onset seizures with or without secondary generalization and were not adequately controlled with one to three concomitant AEDs. Two-thirds (69 percent) of subjects used two concomitant AEDs and 28 percent used one concomitant AED. The most commonly used AEDs were carbamazepine (50 percent), lamotrigine (24 percent), valproic acid (21 percent), and levetiracetam (18 percent). Oxcarbazepine was not allowed as a concomitant AED. Following an eight-week baseline phase that established baseline seizure frequency, subjects were randomized and then entered a treatment period consisting of an initial titration phase (two weeks), and a subsequent maintenance phase (12 weeks). The titration schedule differed amongst the three studies. Thus, patients were started on a daily dose of 400 mg or 800 mg and subsequently increased by 400 mg/day following one or two weeks, until the final daily target dose of 800 mg or 1,200 mg was achieved. Studies 1 and 2 compared eslicarbazepine

acetate doses of 400, 800, and 1,200 mg once daily with placebo, and study 3 compared dosages of 800 and 1,200 mg once daily with placebo. The mean standardized seizure frequency during the maintenance phase over 28 days was the primary efficacy endpoint in all three trials. Eslicarbazepine acetate 400 mg/day was studied in Studies 1 and 2 and did not show a significant treatment effect. At doses of 800 mg/day mean seizure frequency was lower with eslicarbazepine acetate compared to placebo in Studies 1 (five versus 6.6, p=0.047), and Study 2 (6.2 versus 8.6, p=0.006), but not in Study 3 (6.5 versus 7.9, p=0.058). At 1,200 mg/day, all three studies demonstrated a lower seizure frequency with eslicarbazepine acetate as compared to placebo. Seizure frequencies with eslicarbazepine acetate 1,200 mg/day compared to placebo were (4.3 versus 6.6, p=0.001) in Study 1, (6.6 versus 8.6, p=0.042) in Study 2, and (six versus 7.9, p=0.004) in Study 3.

ezogabine (Potiga) and placebo

The efficacy of ezogabine as adjunctive therapy in partial-onset seizures was established using three multicenter, randomized, double-blind, placebo-controlled trials including 1,239 adult patients.[326] Patients had a mean duration of epilepsy of 22 years and experienced an average of at least four partial-onset seizures with or without secondary generalization per 28 days with no seizure-free period exceeding three to four weeks and were concomitantly taking one to three antiepileptic drugs. The primary endpoint was the percent change in seizure frequency from baseline. Patients were randomized to the total daily maintenance dosages of 600 mg per day, 900 mg per day, or 1,200 mg per day, each administered in three equally divided doses. The median percent reduction in 28-day seizure frequency (baseline to double-blind phase) as compared with placebo was statistically significantly ($p<0.05$) in favor of ezogabine across all 3 studies at doses of 600 mg per day (Study 1), at 900 mg per day (Studies 1 and 3), and at 1,200 mg per day (Studies 2 and 3).

RESTORE 2 was a multicenter, randomized, double-blind, placebo-controlled trial including adults with four or more partial-onset seizures per month receiving one to three antiepileptic drugs was conducted to evaluate median percentage seizure reductions from baseline and responder rates (≥ 50 percent reduction in baseline seizure frequency).[327] Patients received ezogabine titrated to 600 or 900 mg per day divided three times daily over four weeks or placebo and continued during a 12-week maintenance phase. The intention-to-treat population included 538 patients (placebo, n=179; 600 mg, n=181; 900 mg, n=178), 471 of whom (placebo, n=164; 600 mg, n=158; 900 mg, n=149) entered the maintenance phase. Median percentage seizure reductions were significantly greater in ezogabine-treated patients (600 mg, 27.9 percent, p=0.007; 900 mg, 39.9 percent, p<0.001) compared with placebo (15.9 percent). Responder rates were significantly higher in ezogabine-treated patients (600 mg, 38.6 percent, $p < 0.001$; 900 mg, 47 percent, $p < 0.001$) than with placebo (18.9 percent). The most commonly reported (>ten percent) adverse events in the placebo, ezogabine 600 mg per day, and ezogabine 900 mg per day groups were dizziness (seven percent, 17 percent, 26 percent), somnolence (ten percent, 14 percent, 26 percent), headache (15 percent, 11 percent, 17 percent), and fatigue (three percent, 15 percent, 17 percent), respectively.

RESTORE 1 was a multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ezogabine 1,200 mg/day as adjunctive treatment in 306 adults with drug-resistant epilepsy with partial-onset seizures with or without secondary generalization.[328] After a prospective 8-week baseline phase, patients entered an 18-week double-blind treatment period (6-week forced dose titration to 1,200 mg/day in three equally divided doses or placebo, followed by a 12-week maintenance phase). Results were analyzed on an intent-to-treat basis for the entire 18-week period and for patients

reaching the maintenance phase. Median percent reduction in total partial-seizure frequency was 44.3 percent for ezogabine compared with 17.5 percent for placebo (p<0.001) during the 18-week double-blind period; responder rates (≥50 percent reduction in total partial-seizure frequency from baseline) were 44.4 percent versus 17.8 percent (p<0.001) for ezogabine versus placebo, respectively. A total of 256 patients entered the 12-week maintenance phase. For those patients median percent reduction in seizure frequency was 54.5 percent for ezogabine compared with 18.9 percent for placebo (p<0.001). Responder rates were 55.5 percent versus 22.6 percent (p<0.001) for ezogabine versus placebo, respectively. The proportion of patients discontinuing due to treatment-emergent adverse events for ezogabine and placebo was 26.8 percent and 8.6 percent, respectively. The most common treatment-emergent adverse events were dizziness, somnolence, fatigue, confusion, dysarthria, urinary tract infection, ataxia, and blurred vision occurring more frequently with ezogabine than placebo.

oxcarbazepine (Oxtellar XR) and placebo

A phase 3, multicenter, double-blind, randomized, three-arm, parallel group, placebo-controlled study to evaluate the efficacy of oxcarbazepine ER as adjunctive treatment in 366 adults with refractory partial seizures with secondarily generalized seizures, simple partial seizures, or complex partial seizures, as add-on therapy compared to placebo.[329] The study included an 8-week baseline period, followed by a 4-week titration period and 12-week maintenance period. Patients had a mean of at least three recorded partial seizures per 28 days during an 8-week baseline phase, receiving one to three concomitant antiepileptic drugs. Patients were randomized to 1,200 mg (n=122), 2,400 mg (n=123) per day or placebo (n=121), as part of adjunctive therapy over a 4-week titration period, followed by a 12-week maintenance phase. The primary efficacy endpoint was the median percent change in seizure frequency between the baseline and treatment (titration plus maintenance period) phase for each oxcarbazepine ER dose compared to placebo for the intent-to-treat population. Median percent reduction in total partial seizure frequency was 42.9 percent for patients treated with 2,400 mg compared with 28.7 percent for placebo (p=0.003). Median percent seizure reduction in the 1,200 mg group was 32.8 percent, failed to separate from the placebo arm (p=0.078), in spite of a decrease in seizure frequency per 28 days relative to baseline. Responder rates, defined as patients experiencing greater than 50 percent reduction in seizure frequency compared to baseline, were 40.7 percent for the 2,400 mg group, 36.1 percent for the 1,200 mg group, and 28.1 percent for the placebo group. A higher percentage of patients discontinued oxcarbazepine than placebo due to adverse events (23.3 percent versus 11.6 percent). The most common adverse events were dizziness, headache, somnolence, diplopia, nausea and vomiting, occurring more frequently with oxcarbazepine ER than placebo, with a higher percentage in the 2,400 mg group than the 1,200 mg group (69.1 percent, 56.6 percent) respectively. No head to head trials conducted to show efficacy better than IR formulation.

perampanel (Fycompa) and placebo

The efficacy of perampanel in the treatment of partial-onset seizures, with or without secondary generalized seizures, was established in three randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3) involving adult and adolescent patients aged 12 years and older totaling 1,038 patients.[330,331,332,333] Patients in the studies included those not adequately controlled with therapy consisting of one to three concomitant anti-epileptic drugs in trials involving an initial six-week baseline period. During the baseline timeframe, patients were required to have more than five seizures in order to be randomized. The baseline period was then followed by an overall treatment period consisting of a six week titration phase followed by a 13-week maintenance phase (overall

treatment of 19 weeks). Patients included in the three trials had a history of epilepsy symptoms with a mean duration of approximately 21 years along with a median baseline seizure frequency that ranged from 9.3 to 14.3 seizures every 28 days. During the three trials, greater than 85 percent of the included patients had treatment regimens consisting of two to three concomitant anti-epileptic medications with or without concurrent vagal nerve stimulation. Approximately one-half of the patients were taking an anti-epileptic medication that was known to induce the CYP3A4 enzyme, (an enzyme important in perampanel metabolism). The presence of these enzyme-inducing medications resulted in significant serum reductions of perampanel concentrations. Each study evaluated the doses administered for placebo and multiple perampanel doses. In the titration phase of all three trials, perampanel patients received starting doses of 2 mg once daily, with subsequent increases of 2 mg per day on a weekly basis until the final target dose was achieved. If patients were seen to experience adverse events, they were permitted to have dosage reductions to a level that was previously tolerated. The primary endpoint in all three studies was the percent of change in seizure frequency measured over a period of 28 days. Measurements of seizure frequency were evaluated during the treatment period as compared to that seen in the baseline period. The criterion for statistical significance was $p<0.05$. There was a statistically significant decrease in seizure rate observed at doses of 4 mg to 12 mg per day. Notable dose response was seen when the dosage was set at 4 mg to 8 mg per day, (range -13.7 to -20.1 percent) with little additional reduction in seizure frequency seen when dosage was increased to 12 mg per day (-13.7 percent).

topiramate XR (Qudexy XR) and placebo

The efficacy of topiramate XR as adjunctive treatment in adult patients with partial onset seizures was demonstrated in a double-blind, randomized, parallel-group study in patients with history of partial onset seizures, with or without secondary generalization.[334] Patients (n=249) on a stable dose of one to three anti-epileptic drugs (AEDs) entered an eight week baseline period and those who experienced eight or greater partial onset seizures, with or without secondary generalization, and less than 21 consecutive seizure-free days were randomized to topiramate XR or placebo, administered once daily, along with their AEDs. The treatment phase consisted of a three week titration period, where a final dose of topiramate XR 200 mg once daily was ultimately achieved in the treatment group, and an eight week maintenance period. The primary endpoint was the percent reduction in the frequency of partial-onset seizure between baseline and treatment phase. There was a statistically significant decrease in the primary endpoint; the median percent reduction in seizure rate was 39.5 percent in patients taking topiramate XR compared to 21.7 percent in patients taking placebo.

META-ANALYSES

Seizures

The Cochrane Group completed a systematic review to investigate the efficacy and safety of vigabatrin versus carbamazepine monotherapy for epilepsy.[335] They searched multiple databases for randomized controlled trials comparing these two agents. Two reviewers independently assessed trial quality and extracted data. The primary outcome was time to treatment withdrawal. The secondary outcomes were time to achieve six- and 12-month remission after randomization, time to first seizure after randomization, and adverse events. Five studies involving a total of 734 participants were eligible for inclusion. One study was assessed as having good quality while the other four were of poor quality. There was no significant difference favoring either agent in terms of time to treatment withdrawal and

time to achieve six-month remission after dose stabilization from randomization, but results did show a disadvantage for vigabatrin on time to first seizure. Compared with carbamazepine, vigabatrin was associated with more occurrences of weight gain and less occurrences of skin rash and drowsiness. There were no differences in visual field defects and visual disturbances. The authors concluded there is currently insufficient data to address the risk-benefit balance of using vigabatrin versus carbamazepine monotherapy for epilepsy.

Bipolar Disorder

A systematic review of treatment of bipolar disorder included a total of 583 articles and 913 papers for randomized controlled trials.[336] Findings suggest that lithium is a useful agent in the acute manic and maintenance phase. Both first- and second-generation antipsychotics are efficacious in the treatment of acute mania. For bipolar depression, quetiapine (Seroquel®) and olanzapine/fluoxetine (Symbyax®) are also effective for treating bipolar depression, while olanzapine (Zyprexa®), quetiapine, and aripiprazole (Abilify®) are effective during the maintenance phase. Valproate and carbamazepine have antimanic properties, whereas lamotrigine may be preferably effective in the treatment of depression but not mania.

Migraine

A systematic review evaluated anticonvulsants for effectiveness in the prophylaxis of migraine.[337] All prospective, controlled studies of anticonvulsants in prevention of migraines published through April 2006 were evaluated. Anticonvulsants, considered as a class, reduce migraine frequency by about 1.3 attacks per 28 days compared with placebo, and more than double the number of patients for whom migraine frequency is reduced by ≥50 percent relative to placebo. Valproate derivatives (Depakene, Depakote/ER, Stavzor) and topiramate (Topamax) were better than placebo, whereas clonazepam (Klonopin) and lamotrigine (Lamictal) were not. Gabapentin (Neurontin) was included in the review, but more research needs to be completed.

PERTINENT CLINICAL COMPARISONS[338,339,340,341,342,343,344,345,346,347]

There is evidence from clinical trials that carbamazepine (Tegretol, Tegretol XR, Carbatrol), gabapentin, lamotrigine, oxcarbazepine (Trileptal), topiramate, and valproate are efficacious as monotherapy in newly diagnosed patients with either partial or mixed seizure disorders. Newly diagnosed patients can be initiated on standard therapy with older agents or on one of the newer drugs mentioned above. For refractory patients with partial seizures, monotherapy with lamotrigine 500 mg per day (on enzyme inducers) is superior to valproic acid 1,000 mg per day. Immediate release oxcarbazepine (2,400 mg per day) and topiramate (1,000 mg per day) are also effective as monotherapy.

In a post-hoc analysis, data from five comparative, double-blind, single-drug studies to evaluate the efficacy of treatment of patients with partial seizures with oxcarbazepine (Trileptal) versus carbamazepine, phenobarbital, phenytoin (Dilantin, Phenytek), and valproate for approximately one year were pooled to investigate same-patient seizure outcome at six and 12 months.[348] The main conclusion was that response at six months is an excellent predictor of response at 12 months.

For pediatric patients, the pathophysiology of partial seizures is similar to that of adults and will probably respond to the same drugs. However, gabapentin, lamotrigine, oxcarbazepine (Trileptal), and topiramate are the preferred adjunctive therapies in pediatric patients.

Overall, generalized seizures are easily treated, and refractory patients are rare. Topiramate has clinical support for effectiveness in this population, which also extends to pediatrics.

There is evidence that lamotrigine is effective in absence seizures and can be an option for newly diagnosed patients.

Perampanel (Fycompa) is a C-III controlled substance, the barbiturates and benzodiazepines are C-IV; lacosamide (Vimpat), pregabalin (Lyrica), and ezogabine (Potiga) are C-V.

SUMMARY

Anticonvulsants have very little or no direct comparative data in the treatment of seizures or any other indication. Selection of drugs for epilepsy treatment frequently depends on particular seizure type. For instance, carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol) is frequently the first choice for partial seizures. Phenytoin (Dilantin, Phenytek), lamotrigine (Lamictal), valproic acid/divalproex (Depakene, Depakote, Depakote ER, Stavzor), eslicarbazepine acetate (Aptiom), ezogabine (Potiga), perampanel (Fycompa) and immediate-release oxcarbazepine (Trileptal), including once-daily extended-release oxcarbazepine (Oxtellar XR) as adjuvant, are also available. The drugs typically chosen first to treat generalized seizures are valproic acid/divalproex, phenytoin, and carbamazepine. For the treatment of absence seizures, valproic acid/divalproex and ethosuximide (Zarontin) are the agents most frequently selected. Valproic acid/divalproex has become utilized the most for patients with combined seizure disorders because it has demonstrated efficacy against many seizure types, such as generalized and partial seizures, in addition to absence seizures. The agents available for use in Lennox-Gastaut Syndrome are lamotrigine (Lamictal), topiramate (Qudexy XR, Topamax, Trokendi XR), rufinamide (Banzel), felbamate (Felbatol), clobazam (Onfi), and clonazepam (Klonopin). Felbamate should be reserved for use if all other options have been exhausted, and the benefits outweigh the risks of aplastic anemia and hepatotoxicity. Vigabatrin (Sabril) is the only anticonvulsant agent in this review that is indicated for the treatment of infantile spasms. Diazepam rectal gel is indicated for the management of selected, refractory patients on stable regimens of AEDs who require intermittent use to control episodes of increased seizure activity.

Many drug interactions exist for the anticonvulsants including interactions among adjunctive anticonvulsants. Phenobarbital, phenytoin, primidone (Mysoline), and carbamazepine are potent inducers of CYP 450 and other enzyme systems.

About 70 percent of patients can be maintained on one drug but not all are seizure-free. The most common reason for treatment failure is noncompliance, which may occur in up to 60 percent of patients. If control is not achieved with one drug, an alternative medication should be attempted before others are added to current therapy. Reduced renal function can lead to an accumulation of renally excreted anticonvulsants, such as gabapentin, topiramate, levetiracetam (Keppra, Keppra XR), and pregabalin (Lyrica). Gabapentin (Neurontin), topiramate, and levetiracetam are preferred for treatment of patients with hepatic dysfunction whereas valproate and felbamate are potentially hepatotoxic and should be avoided in these patients.

Utilization of anticonvulsants in epileptic women who use oral contraceptives, who desire to become pregnant, or who are pregnant require considerations related to drug interactions and pregnancy risk factors. The elderly population also requires special considerations related to medication selection and dosage due to age-related factors and their utilization of multiple medications for comorbidities.

It is difficult to make distinctions amongst any of these drugs for any FDA-approved indication. There are small amounts of comparative data, but extensive clinical trials between the agents have not been done. Overall, the agents have similar efficacy with the newer drugs having fewer serious adverse effects and drug interactions.

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